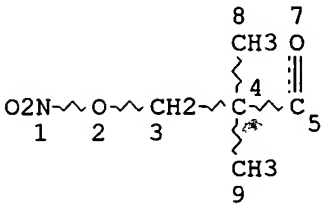
Audet, M.
10/760672

(FILE 'REGISTRY' ENTERED AT 12:04:26 ON 15 APR 2005)
L1 STR

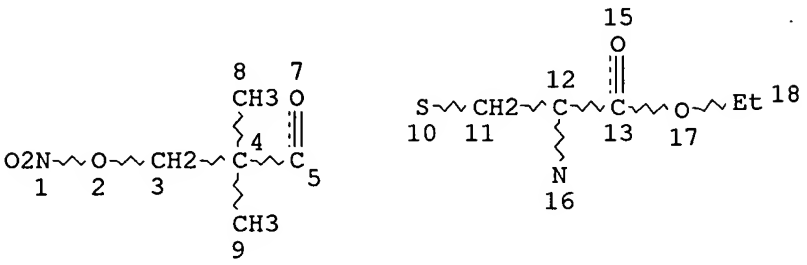


Str.

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 8

STEREO ATTRIBUTES: NONE
L2 (115) SEA FILE=REGISTRY SSS FUL L1
L3 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L4 21 SEA FILE=REGISTRY SUB=L2 SSS FUL L3

100.0% PROCESSED 49 ITERATIONS 21 ANSWERS
SEARCH TIME: 00.00.01

FILE 'CAPLUS' ENTERED AT 12:20:21 ON 15 APR 2005
L5 37 S L4

L5 ANSWER 1 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:875157 CAPLUS
DOCUMENT NUMBER: 139:358773
TITLE: Novel use of guanylate cyclase activators for the treatment of respiratory insufficiency
INVENTOR(S): Grimminger, Friedrich Josef; Schermuly, Ralph; Schudt, Christian
PATENT ASSIGNEE(S): Altana Pharma Ag, Germany
SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003090870	A1	20031106	WO 2003-EP4243	20030424
W: AE, AL, AU, BA, BR, CA, CN, CO, CU, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, RO, SG, TN, UA, US, VN, YU, ZA, ZW				
RW: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR				
EP 1356849	A1	20031029	EP 2002-9552	20020426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CA 2484089	AA	20031106	CA 2003-2484089	20030424
EP 1501605	A1	20050202	EP 2003-722539	20030424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.:

EP 2002-9552	A	20020426
WO 2003-EP4243	W	20030424

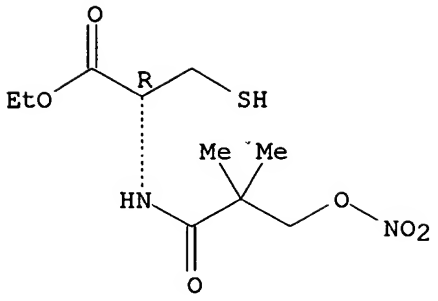
AB The invention relates to the novel use of guanylate cyclase activators for the treatment of partial and global respiratory failure. The object of the present invention is thus to provide a substance which, on oral, i.v. or else inhalational administration, leads on the one hand to the preferred dilatation of vessels in the pulmonary circulation (pulmonary selectivity) and, at the same time, to a redistribution of the blood flow within the lung in favor of the well-ventilated areas (intrapulmonary selectivity). It has now been found, surprisingly, that guanylate cyclase activators are suitable for the treatment of patients having the abovementioned mismatch. Administration of guanylate cyclase activators leads to dilatation of vessels in the pulmonary circulation and, at the same time, to a redistribution of the blood flow within the lung in favor of the well-ventilated areas. This principle, referred to hereinafter as rematching, leads to an improvement in the gas exchange function both at rest and during phys. exercise.

IT **130432-17-6**, SPM-3672 **139146-66-0**, SPM-5185
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel use of guanylate cyclase activators for treatment of respiratory insufficiency in relation to vasodilating activity and combination with other agents)

RN 130432-17-6 CAPLUS

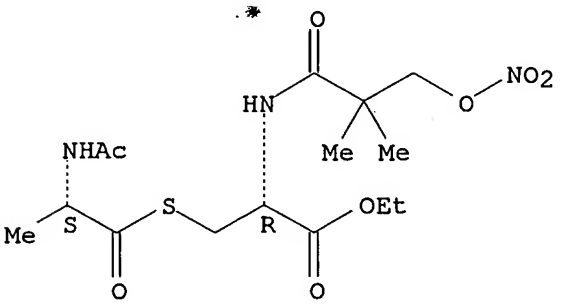
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:132965 CAPLUS
DOCUMENT NUMBER: 138:163603
TITLE: Methods for novel sulfur-containing organic nitrate compds. use in the treatment and prevention of human diseases and conditions
INVENTOR(S): Garvey, David S.; Letts, L. Gordon
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013432	A2	20030220	WO 2002-US24923	20020807
WO 2003013432	A3	20031113		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,

TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1414432 A2 20040506 EP 2002-786354 20020807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
JP 2005501060 T2 20050113 JP 2003-518446 20020807
US 2004152753 A1 20040805 US 2004-760672 20040121
PRIORITY APPLN. INFO.: US 2001-311715P P 20010810
WO 2002-US24923 W 20020807

OTHER SOURCE(S): MARPAT 138:163603

AB The invention describes methods of use for an organic nitrate compound, or a pharmaceutically acceptable salt thereof, wherein the organic nitrate compound comprises at least one sulfur atom and/or at least one disulfide group. The invention also provides methods for treating, preventing and/or reducing inflammation, pain, and fever; for decreasing or reversing the gastrointestinal, renal and other toxicities resulting from the use of nonsteroidal antiinflammatory compds.; for treating and/or preventing gastrointestinal disorders; for treating inflammatory disease states and disorders; for treating and/or preventing ophthalmic diseases or disorders; for treating and/or improving the gastrointestinal properties of COX-2 inhibitors; for facilitating wound healing; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; for decreasing the recurrence of ulcers; for improving gastroprotective properties, anti-Helicobacter pylori properties or antacid properties of proton pump inhibitors; for treating Helicobacter pylori and viral infections. For improving gastroprotective properties of Hz receptor antagonists; for treating and/or preventing inflammations and microbial infections, multiple sclerosis, and viral infections; for treating or preventing restenosis, autoimmune diseases, pathol. conditions resulting from abnormal cell proliferation, polycystic kidney disease, inflammatory diseases or to inhibit wound contraction; for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females; for treating or preventing benign prostatic hyperplasia, hypertension, congestive heart failure, variant (Printzmetal) angina , glaucoma, neurodegenerative disorders, vasospastic diseases, cognitive disorders, urge incontinence, and overactive bladder; for reversing the state of anesthesia. For treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP); for treating respiratory disorders and for treating neurol. conditions.

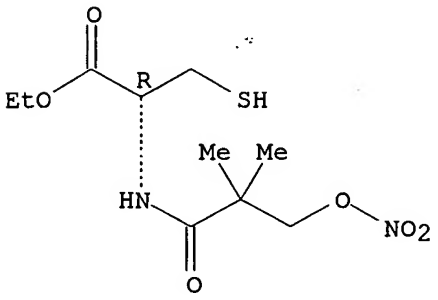
IT **130432-17-6**, SPM 3672 **130432-18-7**
130432-19-8 130432-20-1 130432-21-2
130432-22-3 130432-23-4 139146-65-9, SPM
5186 **139146-66-0**, SPM 5185 **139146-67-1**
167370-45-8 497140-45-1 497140-46-2
497140-47-3 497140-48-4 497140-51-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for novel sulfur-containing organic nitrate compds. use in the treatment and prevention of human diseases and conditions)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester

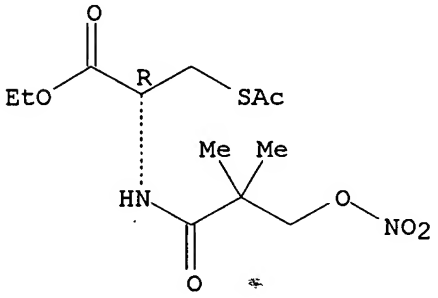
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



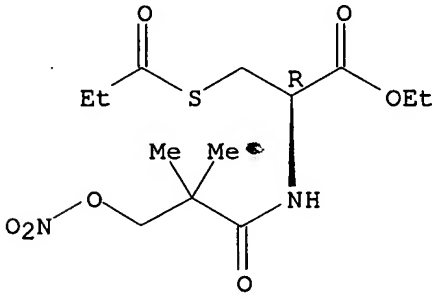
RN 130432-18-7 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, acetate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



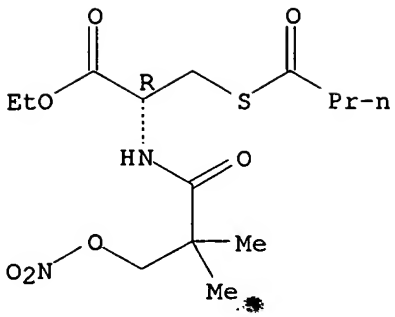
RN 130432-19-8 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, propanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



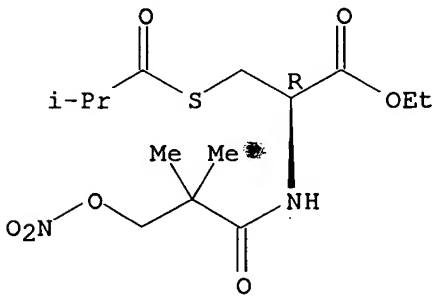
RN 130432-20-1 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, butanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



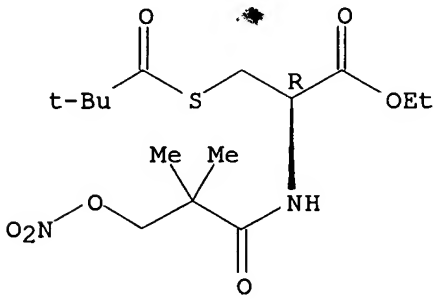
RN 130432-21-2 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, 2-methylpropanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



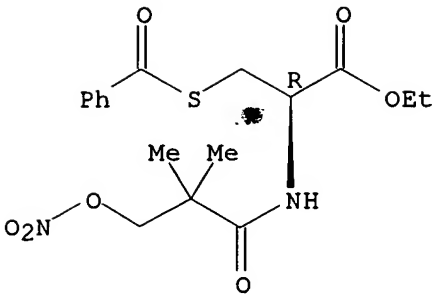
RN 130432-22-3 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, 2,2-dimethylpropanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



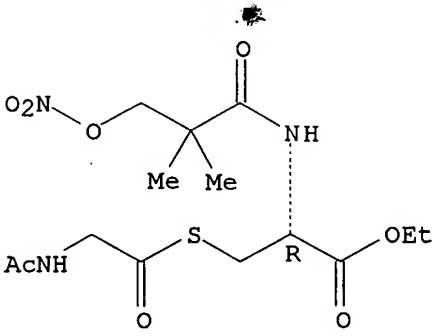
RN 130432-23-4 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, benzoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



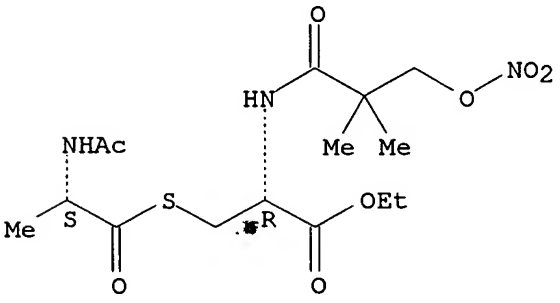
RN 139146-65-9 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetylglycine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



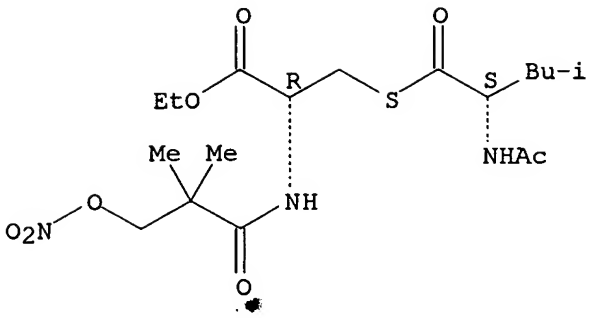
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



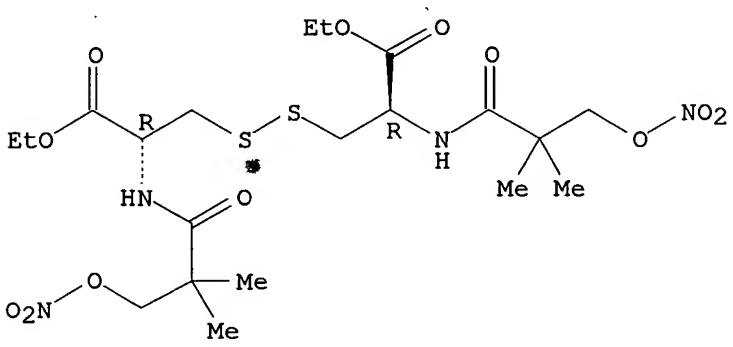
RN 139146-67-1 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-leucine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



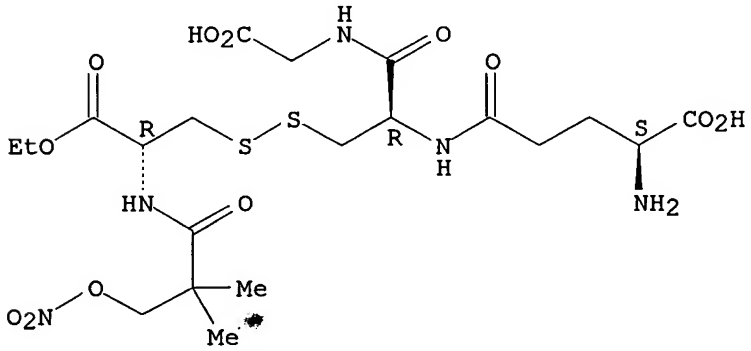
RN 167370-45-8 CAPLUS
CN L-Cystine, N,N'-bis[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, diethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



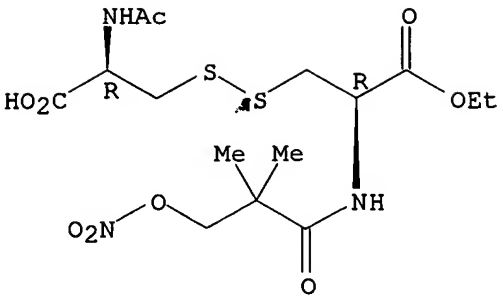
RN 497140-45-1 CAPLUS
CN Glycine, L-γ-glutamyl-L-cysteinyl-, disulfide with N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-L-cysteine ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



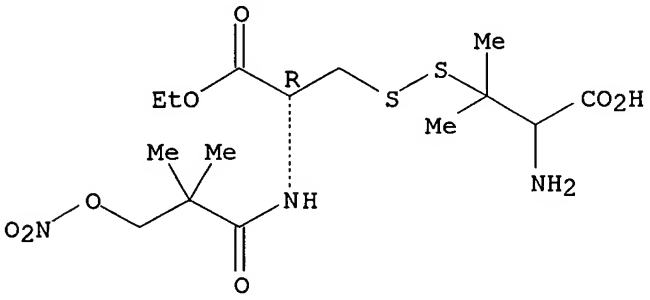
RN 497140-46-2 CAPLUS
CN L-Cystine, N-acetyl-N'-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, 1'-ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



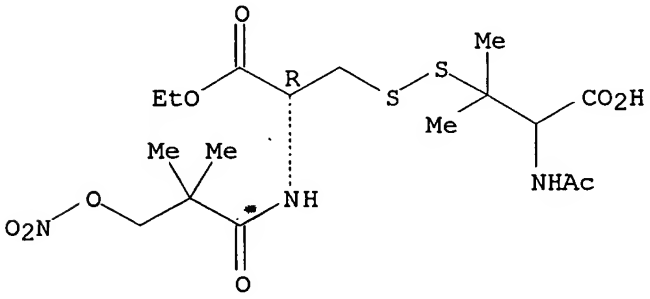
RN 497140-47-3 CAPLUS
CN Valine, 3-[[(2R)-2-[[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]amino]-3-ethoxy-3-oxopropyl]dithio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



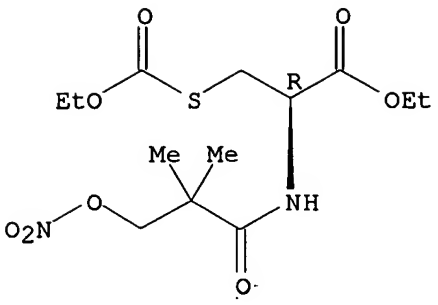
RN 497140-48-4 CAPLUS
CN Valine, N-acetyl-3-[[(2R)-2-[[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]amino]-3-ethoxy-3-oxopropyl]dithio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 497140-51-9 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ethyl carbonate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



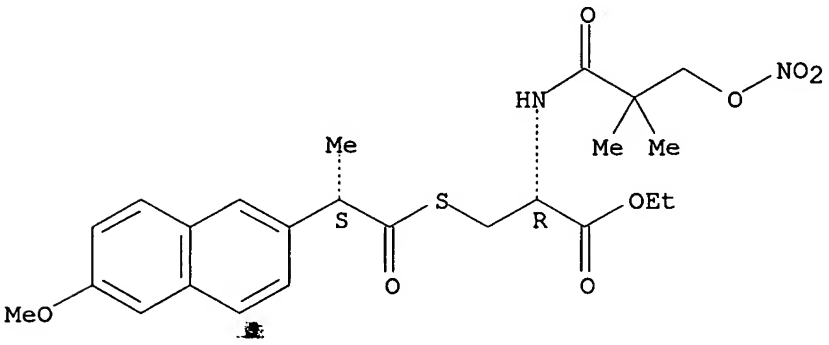
L5 ANSWER 3 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:864914 CAPLUS
DOCUMENT NUMBER: 138:395694
TITLE: NO-donors (VII [1]): synthesis and cyclooxygenase inhibitory properties of N- and S-nitrooxypivaloyl-cysteine derivatives of naproxen - a novel type of NO-NSAID
AUTHOR(S): Kartasasmita, Rahmana E.; Laufer, Stefan; Lehmann, Jochen
CORPORATE SOURCE: Institute of Pharmacy, University of Bonn, Bonn, D-53121, Germany
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (2002), 335(8), 363-366
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nitric oxide (NO) has been reported to subserve many of the same mucosal protection mechanisms as prostaglandins and is sufficient for acute gastroprotection and ulcer healing. In fact, NO-donating NSAID hybrid compds. such as the nitrooxybutyl ester of naproxen show reduced ulcerogenic activity while maintaining anti-inflammatory activity. We introduce two prototypes of novel triple-hybrid compds. consisting of cysteine which is known to enhance the activity of organic nitrates and to reduce nitrate tolerance, an NSAID (naproxen), and an organic nitrate (nitrooxypivaloic acid). L-Cysteine Et ester first was N-acylated in a CH2Cl2/H2O two-phase system using the acid chlorides of naproxen or nitrooxypivaloic acid, resp., and sodium acetate, or alternatively using the DCC-activated nitrooxy acid in absolute CH2Cl2. The N-acylated intermediates were subsequently S-acylated using the acid chlorides or alternatively the carbonyldiimidazole (CDI)-activated acids again. The two naproxen-cysteine-nitrate hybrid prodrugs were screened in vitro for their cyclooxygenase inhibitory properties relative to naproxen. In this screening the N-nitrooxyacylcysteine derivative was found to be inactive in the concentration range of 0.1-10 μmol/L against both COX-1 and COX-2, while the S-nitrooxyacylcysteine derivative had only weak activity against COX-1.

IT **531557-47-8P 531557-48-9P**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and cyclooxygenase inhibitory properties of novel NO-NSAID nitrooxypivaloyl-cysteine derivs. of naproxen)
RN 531557-47-8 CAPLUS

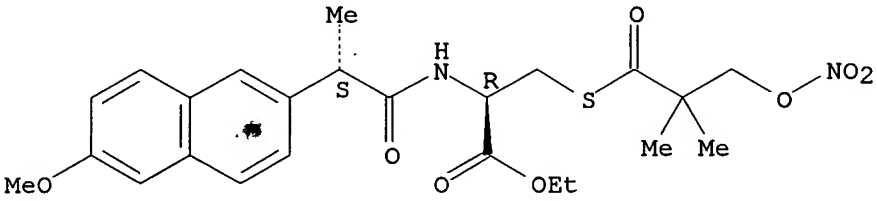
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, (αS)-6-methoxy-α-methyl-2-naphthaleneacetate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



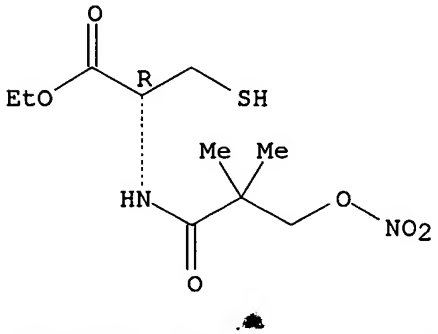
RN 531557-48-9 CAPLUS
CN L-Cysteine, N-[(2S)-2-(6-methoxy-2-naphthalenyl)-1-oxopropyl]-, ethyl ester, 2,2-dimethyl-3-(nitrooxy)propanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **130432-17-6P**
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and cyclooxygenase inhibitory properties of novel NO-NSAID nitrooxypivaloyl-cysteine derivs. of naproxen)
RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR

THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

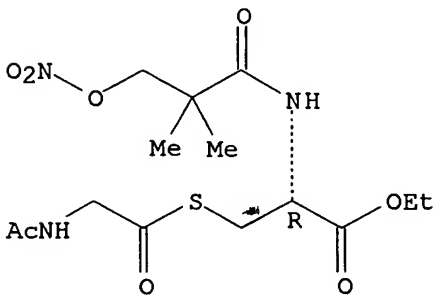
L5 ANSWER 4 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:227619 CAPLUS
DOCUMENT NUMBER: 135:29010
TITLE: Inhibition of peroxynitrite-induced dityrosine formation with oxidized and reduced thiols, nitric oxide donors, and purine derivatives
AUTHOR(S): Ferdinandy, Peter; Schulz, Richard
CORPORATE SOURCE: Department of Biochemistry, Cardiovascular Research Group, University of Szeged, Szeged, H-6720, Hung.
SOURCE: Antioxidants & Redox Signaling (2001), 3(1), 165-171
CODEN: ARSIF2; ISSN: 1523-0864
PUBLISHER: Mary Ann Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peroxynitrite, formed by the combination of superoxide anion and nitric oxide, is a powerful oxidant at physiol. pH and is apparently involved in the pathogenesis of several human diseases. Therefore, inhibitors of peroxynitrite-induced oxidation are important targets for pharmaceutical development. The reaction of peroxynitrite with L-tyrosine, one of its biol. targets, yields stable products, including nitrotyrosine and dityrosine. Here we test the ability of thiols, nitric oxide donors, and purine derivs. to inhibit peroxynitrite-induced dityrosine formation in a physiol. buffer containing bicarbonate/CO2. We show that both reduced and oxidized thiols, nitric oxide donors, and urate, but not other purine derivs., reduce peroxynitrite-induced dityrosine formation.

IT **139146-65-9**, SP/W-5186
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of peroxynitrite-induced dityrosine formation with oxidized and reduced thiols, nitric oxide donors, and purine derivs.)

RN 139146-65-9 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetylglycine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searcher : Shears 571-272-2528

L5 ANSWER 5 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:785898 CAPLUS
DOCUMENT NUMBER: 133:329627
TITLE: Tetracyclic cGMP-specific phosphodiesterase inhibitors and their use in disease treatment
INVENTOR(S): Daugan, Alain Claude Marie; Gellibert, Francoise
PATENT ASSIGNEE(S): Icos Corp., USA
SOURCE: U.S., 30 pp., Cont.-in-part of PCT 9519978.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

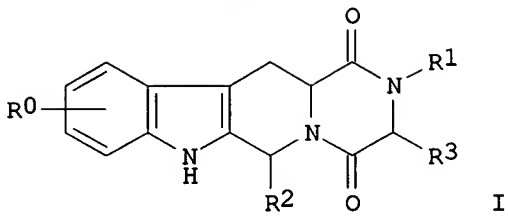
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6143746	A	20001107	US 1998-154051	19980916
WO 9519978	A1	19950727	WO 1995-EP183	19950119
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
WO 9703675	A1	19970206	WO 1996-EP3024	19960711
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
WO 9703985	A1	19970206	WO 1996-EP3025	19960711
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
US 6025494	A	20000215	US 1998-133078	19980812
CA 2340636	AA	20000323	CA 1999-2340636	19990826
EP 1113800	A1	20010711	EP 1999-945201	19990826
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002524516	T2	20020806	JP 2000-569812	19990826
US 6127542	A	20001003	US 1999-399667	19990921
US 6369059	B1	20020409	US 2000-633431	20000807
CZ 289832	B6	20020417	CZ 2000-3428	20000919
US 2002119976	A1	20020829	US 2002-68114	20020205
US 6784179	B2	20040831		
JP 2004217674	A2	20040805	JP 2004-125881	20040421

PRIORITY APPLN. INFO.:		
GB 1994-1090	A	19940121
WO 1995-EP183	A2	19950119
GB 1995-14464	A	19950714
GB 1995-14465	A	19950714

WO 1996-EP3024	A2	19960711
WO 1996-EP3025	A2	19960711
JP 1995-519339	A3	19950119
CZ 1998-33	A3	19960711
US 1996-669389	A3	19960716
US 1998-133078	A1	19980812
US 1998-154051	A	19980916
WO 1999-US19466	W	19990826
US 1999-399667	A1	19990921
US 2000-633431	A1	20000807

OTHER SOURCE(S): MARPAT 133:329627

GI



I

AB A compound of formula I (R0 = H, halogen, C1-6 alkyl; R1 = H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo-C1-6 alkyl, C3-8 cycloalkyl, C3-8 cycloalkyl-C1-3 alkyl, aryl-C1-3 alkyl, heteroaryl-C1-3 alkyl; R2 = (substituted) monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or (substituted) bicyclic ring (a) attached to the rest of the mol. via one of the benzene ring carbon atoms, and wherein the fused ring is a 5- or 6-membered ring which may be saturated or partially or fully unsatd., and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulfur, and nitrogen; R3 = H, C1-3 alkyl, or R1 and R3 together = 3- or 4-membered alkyl or alkenyl chain) and salts and solvates thereof is disclosed. Compound I is a potent and selective inhibitor of cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase, having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders and erectile dysfunction. Thus, many I compds. were synthesized and tested in vitro as inhibitors of cGMP phosphodiesterase. Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione showed IC50 of 10 nM.

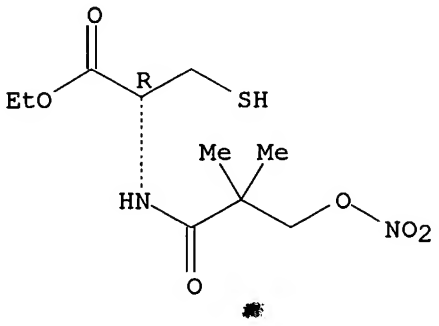
IT **130432-17-6**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug containing phosphodiesterase inhibitor and; tetracyclic cyclic GMP-specific phosphodiesterase inhibitors and their use in disease treatment)

Searcher : Shears 571-272-2528

RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:779769 CAPLUS
DOCUMENT NUMBER: 134:80692
TITLE: Inhibition of endothelial cell activation by nitric oxide donors
AUTHOR(S): Zampolli, Antonella; Basta, Giuseppina; Lazzerini, Guido; Feelisch, Martin; De Caterina, Raffaele
CORPORATE SOURCE: Consiglio Nazionale delle Ricerche Institute of Clinical Physiology Laboratory for Thrombosis and Vascular Research, Pisa, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 295(2), 818-823
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

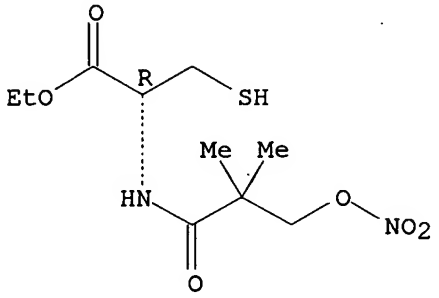
AB Because nitric oxide (NO) inhibits the expression of endothelial leukocyte adhesion mols., NO-generating compds. have major therapeutic potential for use outside their classical indications. We report on the in vitro potential antiatherogenicity of two novel cysteine-containing NO donors, SP/W 3672, a fast spontaneous NO releaser, and its prodrug SP/W 5186, which liberates NO after bioactivation. The ability of these two compds. to inhibit monocyte adhesion and surface expression of endothelial adhesion mols. was evaluated and compared with that of other NO donors. SP/W 5186 and SP/W 3672 inhibited the adhesion of U937 monocytes to cultured human endothelial cells more potently than S-nitrosoglutathione (GSNO) or spermine NONOate, whereas nitroglycerin and isosorbide dinitrate were ineffective at comparable concns. A similar rank order of potency was found for the inhibition of expression of the adhesion mols. vascular cell adhesion mol.-1, intercellular adhesion mol.-1, and E-selectin as well as for major histocompatibility complex class II antigen expression. Estimated IC50 values for vascular cell adhesion mol.-1 were >400 μM for SP/W 4744 (control for SP/W 3672 lacking the cysteine moiety), 200 μM for GSNO and spermine NONOate, 80 μM for SP/W 3672, and 50 μM for SP/W 5186. Moreover, SP/W 5186 inhibited VCAM-1 mRNA levels more

potently than GSNO. This effect was likely to be transcriptional because mRNA degradation was not affected. In conclusion, SP/W 3672 and SP/W 5186 are novel potent inhibitors of endothelial activation, and this effect appears to relate to their ability to liberate NO for prolonged periods of time, either spontaneously or after conversion to active hydrolytic products.

IT **130432-17-6**, SP/W 3672 **139146-65-9**, SP/W 5186
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of endothelial cell activation by nitric oxide donors)

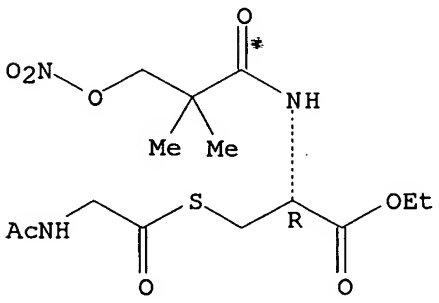
RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139146-65-9 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetylglycine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:464048 CAPLUS
DOCUMENT NUMBER: 131:82989
TITLE: Nitric oxide-releasing chelating agents and their therapeutic use
INVENTOR(S): Towart, Robertson; Karlsson, Jan Olof Gustav; Wistrand, Lars Goran; Malmgren, Hakan
PATENT ASSIGNEE(S): Nycomed Imaging A/S, Norway

SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9933823	A1	19990708	WO 1998-GB3840	19981218
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9917702	A1	19990719	AU 1999-17702	19981218
EP 1060174	A1	20001220	EP 1998-962567	19981218
EP 1060174	B1	20040922		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001527072	T2	20011225	JP 2000-526505	19981218
AT 277038	E	20041015	AT 1998-962567	19981218
ZA 9811825	A	19990708	ZA 1998-11825	19981223
US 6391895	B1	20020521	US 2000-599862	20000623

PRIORITY APPLN. INFO.:
GB 1997-27226 A 19971223
US 1998-76793P P 19980304
GB 1998-5450 A 19980313
WO 1998-GB3840 W 19981218

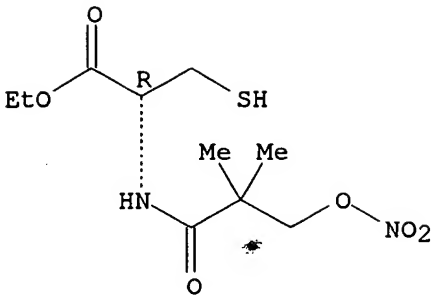
OTHER SOURCE(S): MARPAT 131:82989

AB Chelating agents, in particular dipyridoxyl and aminopolycarboxylic acid-based chelating agents, and their metal chelates, when linked directly or indirectly to at least one nitric oxide-releasing moiety, or when use in combination with nitric oxide or a nitric oxide-releasing moiety, have been found to be effective in treating a variety of disorders. In particular, such compds. may be used in treating conditions associated with the presence of free radicals in the body, e.g. reperfusion injuries, and in reducing the cardiotoxicity of anti-tumor agents, e.g. anthracyclines and/or paclitaxel.

IT **130432-17-6D**, SPM 3672, chelating agent conjugates
139146-66-0D, SPM 5185, chelating agent conjugates
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-releasing chelating agents, and therapeutic use)

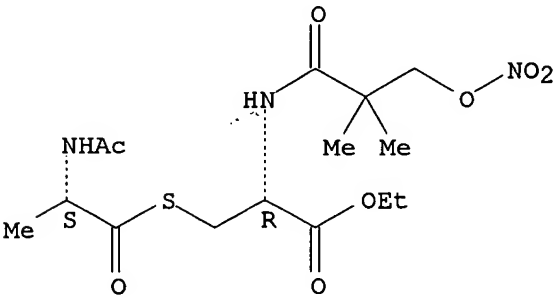
RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

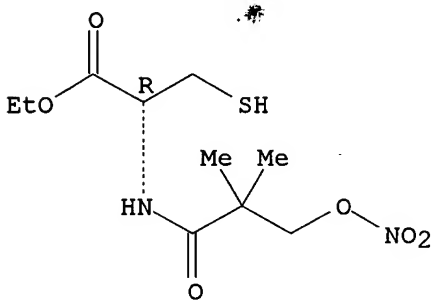
L5 ANSWER 8 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:51345 CAPLUS
DOCUMENT NUMBER: 130:276039
TITLE: SP/W-5186: a novel sulfhydryl-containing NO donor
AUTHOR(S): Bonn, R.; Scharfenecker, U.; Friehe, H.; Gerloff, J.
CORPORATE SOURCE: Research and Development, Schwarz Pharma AG, Monheim am Rhein, D-40789, Germany
SOURCE: Cardiovascular Drug Reviews (1998), 16(3), 195-211
CODEN: CDREEA; ISSN: 0897-5957
PUBLISHER: Neva Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 54 refs. The prodrug SP/W-5186 and its active principle SP/W-3672 are new NO donors designed for the prophylaxis of angina pectoris without nitrate tolerance. The hybrid mol. SP/W-3672 contains a nitrate group and a free sulfhydryl group and should, therefore, generate NO to activate soluble GC in the absence of endogenous thiols. Due to the instability of the free SH groups, this compound is administered orally as the stable prodrug SP/W-5186, in which the SH group is protected by acylation with N-acetylglycine. Pharmacol. in vitro studies on the mechanism of action of SP/W-3672 showed that this drug has-50-fold higher activity than isosorbide mononitrate (ISMN). In vivo studies with SP/W-5186 in healthy

volunteers showed nitrate-like hemodynamic effects at doses of 150 mg. This dose was equieffective with ISMN 20 mg in the magnitude of the effect, but of shorter duration. In angina pectoris patients no antianginal effects were obtained at single doses up to 120 mg. The discrepancy between a nitrate-like activity from in vitro and in vivo studies was not caused by incomplete absorption, but presumably by rapid biotransformation of the active metabolite M1 (SP/W-3672) into the hydrophilic, but less active, metabolite M2 (SP/W-4853), which is excreted rapidly by the kidneys. Pharmacokinetic modeling points to an administration schedule of 120 mg six times daily in order to ensure a 24-h effect, which negates any theor. advantage of the absence of nitrate tolerance of SP/W-5186 in comparison to tolerance-free interval therapy with isosorbide dinitrate or ISMN. It is concluded that to create a new nitrate through hybridization of an NO donor with a SH group resulted in a drug with lack of efficacy up to 120 mg.

IT **130432-17-6**, SP/W 3672 **139146-65-9**, SP/W-5186
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetics and pharmacol. of SP/W-5186 as a novel sulfhydryl-containing nitric oxide donor)

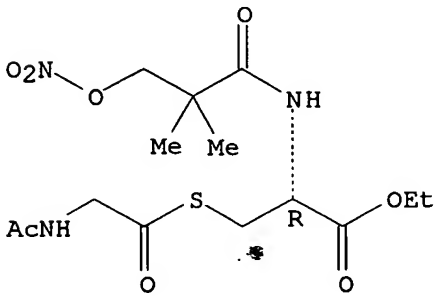
RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139146-65-9 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetylglycine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



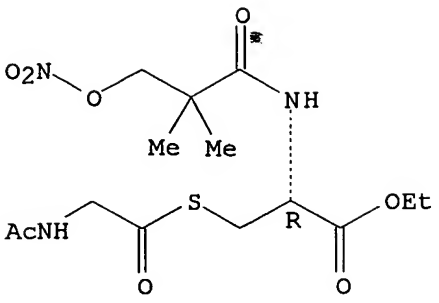
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:743852 CAPLUS
DOCUMENT NUMBER: 130:119335
TITLE: SP/W-5186, a cysteine-containing nitric oxide donor, attenuates postischemic myocardial injury
AUTHOR(S): Liu, Gao-Lin; Christopher, Theodore A.; Lopez, Bernard L.; Gao, Feng; Guo, Yaping; Gao, Erhe; Knuettel, Karlheinz; Feelisch, Martin; Ma, Xin L.
CORPORATE SOURCE: Division of Emergency Medicine, Thomas Jefferson University, Pharmacia AG, Monheim, Germany
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1998), 287(2), 527-537
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Lippencott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of SP/W-5186, a cysteine-containing nitric oxide (·NO) donor, on myocardial reperfusion injury were studied in a rabbit ischemia (45 min) and reperfusion (180 min) model. Five min before reperfusion, either low-dose (0.3 μmol/kg) or high-dose (1 μmol/kg) SP/W-5186 was given i.v. as a bolus. Administration of 0.3 μmol/kg SP/W-5186 did not change mean arterial blood pressure, heart rate or pressure-rate index. However, administration of low-dose SP/W-5186 exerted marked cardioprotective effects as evidenced by improved cardiac functional recovery ($P < .05$ vs. vehicle), decreased plasma creatine kinase concentration ($P < .01$) and reduced infarct size ($P < .01$). Moreover, administration of SP/W-5186 significantly decreased platelet aggregation ($P < .01$ vs. vehicle), attenuated polymorphonuclear leukocyte (PMN) accumulation in myocardial tissue, inhibited PMN adhesion to endothelial cells and preserved endothelial function. Administration of high-dose SP/W-5186 resulted in a transient but significant decrease in mean arterial blood pressure and exerted more cardiac protection compared with low-dose treatment. However, the effects on platelet aggregation, PMN accumulation and PMN adhesion did not differ significantly between the two SP/W-5186 groups. Furthermore, administration of SP/W-6373, an analog of SP/W-5186 that lacks the NO moiety, failed to exert any protective effects. These results demonstrate that NO released from SP/W-5186 significantly protected myocardial tissue from reperfusion injury. The primary mechanisms of the observed cardioprotection by SP/W-5186 involve inhibition of platelet aggregation, attenuation of PMN-endothelium interaction and preservation of endothelial function.

IT **139146-65-9**, SP/W 5186
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cysteine-containing nitric oxide donor SP/W-5186 attenuates postischemic myocardial injury)
RN 139146-65-9 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetylglycine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:163801 CAPLUS
DOCUMENT NUMBER: 128:205139
TITLE: Preparation of S- and O-nitratoacyl compounds as inhibitors of thrombocyte aggregation
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Ger. Offen., 6 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

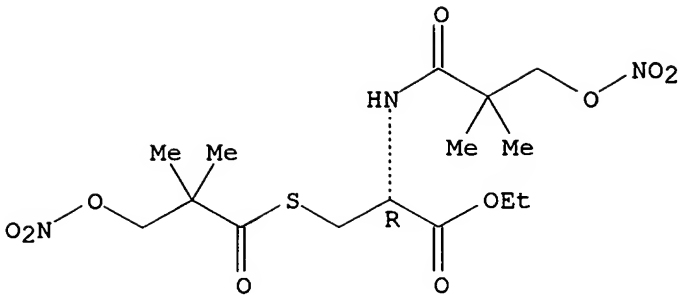
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19634793	A1	19980305	DE 1996-19634793	19960829
PRIORITY APPLN. INFO.:			DE 1996-19634793	19960829

AB Nitratoacyl compds., e.g., N,O-bis[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-L-serine Et ester (I), were prepared as inhibitors of thrombocyte aggregation. Thus, amino acid derivative I, prepared by acylation of O-(3-nitratopivaloyl)-L-serine Et ester with 3-nitratopivaloyl chloride, inhibited collagen-induced thrombocyte aggregation with IC50 = 5.9±1.2 μM.

IT **204076-83-5P 204076-89-1P 204076-90-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of S- and O-nitratoacyl compds. as inhibitors of thrombocyte aggregation)

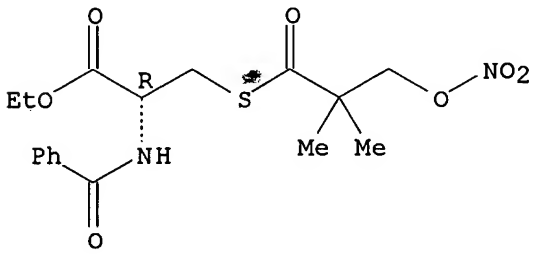
RN 204076-83-5 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, 2,2-dimethyl-3-(nitrooxy)propanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



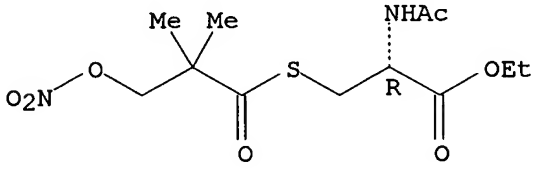
RN 204076-89-1 CAPLUS
CN L-Cysteine, N-benzoyl-, ethyl ester, 2,2-dimethyl-3-(nitrooxy)propanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



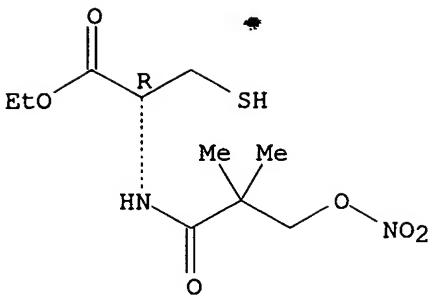
RN 204076-90-4 CAPLUS
CN L-Cysteine, N-acetyl-, ethyl ester, 2,2-dimethyl-3-(nitrooxy)propanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **130432-17-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of S- and O-nitratoacyl compds. as inhibitors of thrombocyte aggregation)
RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:524490 CAPLUS
DOCUMENT NUMBER: 127:214847
TITLE: The effect of chronic treatment with NO donors during intimal thickening and fatty streak formation
AUTHOR(S): De Meyer, Guido R.Y.; Bult, Hidde; Kockx, Mark M.; Herman, Arnold G.
CORPORATE SOURCE: Division of Pharmacology, University of Antwerp, Antwerp, B-2610, Belg.
SOURCE: BioFactors (1997), 6(2), 209-215
CODEN: BIFAEU; ISSN: 0951-6433
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Intimal thickening in arteries is considered as a site of predilection for atherosclerosis. We investigated whether oral application of the nitric oxide (NO) donors SPM-5185 (N-nitratopivaloyl-S-(N'-acetylalanyl)-cysteine ethylester, 10 mg/kg body weight/b.i.d.) and molsidomine (prodrug of 3-morpholino-sydnonimine (SIN-1), 10 mg/kg body weight/day) can retard intimal thickening and changes in vascular reactivity induced by a silicone collar positioned around the carotid artery of rabbits. Intimal thickening was significantly inhibited by SPM-5185 (cross-sectional area 18±6 vs. 44±10 + 10-3 mm2; $P < 0.05$), but not by molsidomine (28±6 vs. 35±9 + 10-3 mm2), which is a donor of both NO and superoxide anions. In organ chamber studies collaring was associated with a decreased sensitivity to acetylcholine (ACh). SPM-5185 evoked a tendency towards normalization of the pD2 of ACh in collared arteries. We also investigated whether chronic nitric oxide (NO) treatment affected vascular reactivity and fatty streak development in the rabbit aorta. During 16 wk rabbits received 150 g/day of a standard diet, or diets with 0.3% cholesterol, with 0.02% molsidomine (10 mg/kg body weight/day) or with the combination. The NO donor enhanced the area of fatty streaks, without affecting hypercholesterolemia. Moreover, it desensitized the smooth muscle cells of the rabbit aorta to vasodilators acting via the cytoplasmic guanylate cyclase and suppressed the capacity of the endothelial cells to release NO in response to muscarinic receptor stimulation. This suggested that chronic exposure to large quantities of NO caused a neg. feedback, with selective decreases of both the endothelial capacity to generate NO and the responsiveness to vasodilators operating via cyclic GMP. In conclusion, we demonstrated

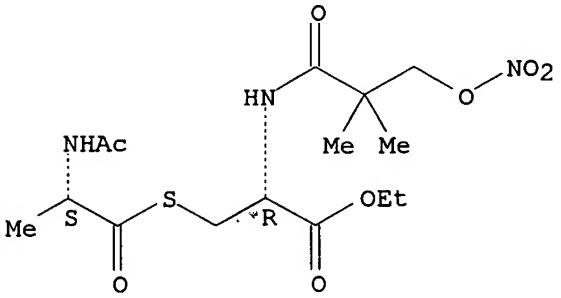
that exogenous NO can decrease intimal hyperplasia in vivo. However, prolonged in vivo treatment with a donor of NO enhanced atherosclerosis in hypercholesterolemic rabbits.

IT **139146-66-0**, SPM-5185
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of chronic treatment with NO donors during intimal thickening and fatty streak formation)

RN 139146-66-0 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:324420 CAPLUS

DOCUMENT NUMBER: 125:48752

TITLE: Biochemical and pharmacological characterization of the novel NO-donor, SP/W-5186

AUTHOR(S): Knuettel, Karlheinz; Meese, Claus O.; Boekens, Hilmar; Spahr, Rolf; Friehe, Hugo; Rees, Daryl; Follenfant, Michael J.; Whittle, Brendan J. R.; Feelisch, Martin

CORPORATE SOURCE: Schwarz Pharma AG, Monheim, D-40789, Germany

SOURCE: Portland Press Proceedings (1996), 10(Biology of Nitric Oxide Part 5), 189
CODEN: POPPEF; ISSN: 0966-4068

PUBLISHER: Portland Press

DOCUMENT TYPE: Journal

LANGUAGE: English

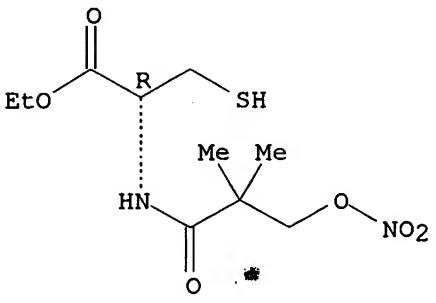
AB SP/W-5186 is rapidly metabolized to the active principle SP/W-3672 which spontaneously generates NO. Both SP/W-5186 and SP/W-3672 have considerably more potent vasorelaxant and anti-platelet activity than classical organic nitrates. SP/W-5186 elicits long-acting hemodynamic effects and is associated with a low tendency of tolerance development in vivo.

IT **130432-17-6**, SP/W 3672
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(biochem. and pharmacol. characterization of NO-donor SP/W-5186)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

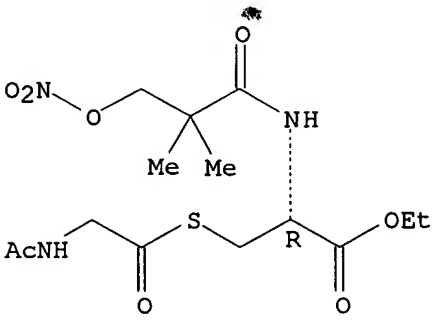


IT **139146-65-9**, SPM 5186
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biochem. and pharmacol. characterization of NO-donor SP/W-5186)

RN 139146-65-9 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetylglycine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 13 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:215187 CAPLUS

DOCUMENT NUMBER: 124:306942

TITLE: Preferential dilation of large coronary microvessels by the mononitrates SPM-4744 and SPM-5185

AUTHOR(S): Wang, Steven Y.; Feelisch, Martin; Harrison, David G.; Sellke, Frank W.

CORPORATE SOURCE: Dep. Internal Med., Emory Univ. Sch. Med. Veterans Administration Med. Cent., Atlanta, GA, USA

SOURCE: Journal of Cardiovascular Pharmacology (1996), 27(4), 587-93
CODEN: JCPCDT; ISSN: 0160-2446

PUBLISHER: Lippincott-Raven

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A novel aspect of the pharmacodynamic action of nitroglycerin is that it is a potent dilator of larger coronary arteries, yet it dilates

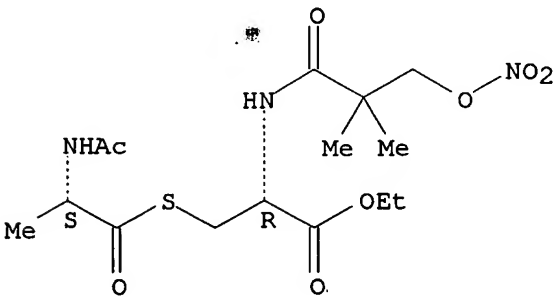
smaller coronary microvessels submaximally and only in high concns. We sought to determine whether this property was shared by other organic nitrates. The effects of two mononitrates, SPM-4744 and SPM-5185 (the latter of which possesses a thioester in its structure), on coronary microvessels of different sizes were studied. Large (200-μm diameter) and small (<100-μm diameter) porcine coronary microvessels were studied in vitro while pressurized in a no-flow state. After constriction with the thromboxane analog U46619, maximal dilations (as a percent of preconstricted tone at the highest applied concentration, 10 μM) of small coronary microvessels were 18 ± 3 and 16 ± 2% in response to SPM-4744 and SPM-5185, resp. The dilations of larger coronary microvessels to SPM-4744 and SPM-5185 were 55 ± 5 and 43 ± 6%, resp. (both $p < 0.001$ vs. the small vessel responses). This pattern of differential vasodilatation of large and small coronary microvessels was similar to that produced by nitroglycerin. In contrast, sodium nitroprusside produced equivalent degrees of vasodilation of small and large coronary microvessels. Addnl. expts. demonstrated that both SPM compds. produced dilation of the coronary microcirculation in isolated rat heart and relaxed isolated segments of rat aortic rings only in high (≥1 μM) concns. These data demonstrate that the organic mononitrates are similar to nitroglycerin in their selectivity for larger coronary microvessels and produce only minimal dilation of coronary microvessels <100 μM in diameter

IT **139146-66-0P**, SPM-5185
RL: SPN (Synthetic preparation); PREP (Preparation)
(preferential dilation of large coronary microvessels by mononitrates SPM-4744 and SPM-5185)

RN 139146-66-0 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 14 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	1995:969653 CAPLUS
DOCUMENT NUMBER:	124:794
TITLE:	Pharmaceutical preparations stimulating nitric oxide formation or release for prevention and treatment of endothelial dysfunction
INVENTOR(S):	Noack, Eike Albrecht; Kojda, Georg
PATENT ASSIGNEE(S):	Isis Pharma GmbH, Germany
SOURCE:	PCT Int. Appl., 36 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9526725	A1	19951012	WO 1995-DE421	19950328
W: AM, AU, BG, BR, BY, CA, CN, CZ, DE, EE, FI, GE, HU, IS, JP, KP, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 4410997	A1	19951026	DE 1994-4410997	19940330
CA 2186783	AA	19951012	CA 1995-2186783	19950328
AU 9521345	A1	19951023	AU 1995-21345	19950328
AU 698359	B2	19981029		
EP 752858	A1	19970115	EP 1995-914275	19950328
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1150387	A	19970521	CN 1995-193401	19950328
HU 76676	A2	19971028	HU 1996-2671	19950328
HU 220165	B	20011128		
JP 09510979	T2	19971104	JP 1995-525343	19950328
LV 11666	B	19970620	LV 1996-378	19960919
FI 9603883	A	19960927	FI 1996-3883	19960927
NO 9604102	A	19960927	NO 1996-4102	19960927
US 5973011	A	19991026	US 1996-721465	19960927
LT 4310	B	19980325	LT 1996-148	19961022
BG 63073	B1	20010330	BG 1996-100930	19961022
PRIORITY APPLN. INFO.:			DE 1994-4410997 A	19940330
			WO 1995-DE421 W	19950328

AB Compds. which release or transfer NO, endogenous NO formation stimulators, and guanylate cyclase stimulators are useful for preventing, treating, and eliminating vascular endothelial dysfunction and associated diseases. The endothelial dysfunction may result from hypercholesteremia, hypoxia, mech. damage from angiog., reperfusion, hypertension, diabetic angiopathy, etc. Thus, pentaerythrityl tetranitrate (6 mg/kg/day in the feed) protected rabbits maintained on cholesterol-enriched feed from development of atherosclerotic lesions and from loss of the acetylcholine-induced, endothelium-mediated vasorelaxation response. Tablets were prepared containing pentaerythrityl tetranitrate 20, lactose 137, potato starch 80, gelatin 3, talc 22, Mg stearate 5, and highly disperse SiO2 6 mg.

IT **130432-17-6**, ~~SPM 3672~~

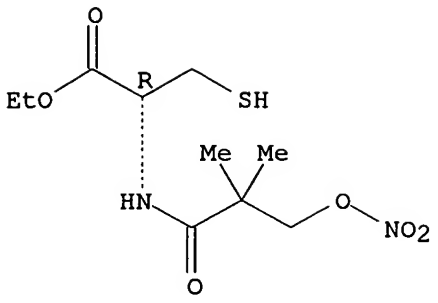
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmaceutical prepns. stimulating nitric oxide formation or release for prevention and treatment of endothelial dysfunction)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 15 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:962334 CAPLUS
DOCUMENT NUMBER: 124:45238
TITLE: Specificity of different organic nitrates to elicit NO formation in rabbit vascular tissues and organs in vivo
AUTHOR(S): Muelsch, Alexander; Bara, Agnes; Mordvintcev, Peter; Vanin, Anatol; Busse, Rudi
CORPORATE SOURCE: Zentrum der Physiologie, Universitaet Frankfurt, Frankfurt, D-60590, Germany
SOURCE: British Journal of Pharmacology (1995), 116(6), 2743-9
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

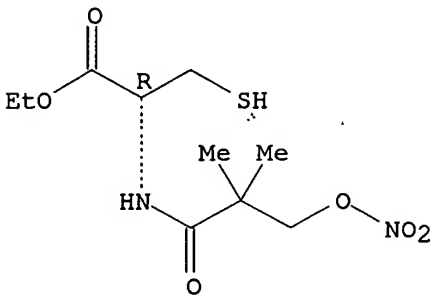
AB In the present study we assessed the formation of nitric oxide (NO) from classical and thiol-containing organic nitrates in vascular tissues and organs of anesthetized rabbits, and established a relationship between the relaxant response elicited by nitroglycerin (NTG) and NO formation in the rabbit isolated aorta. Furthermore, the effect of isolated cytochrome P 450 on NO formation from organic nitrates was investigated. Rabbits received diethyldithiocarbamate (DETC; 200 mg kg-1 initial bolus i.p. and 200 mg kg-1 during 20 min, i.v.) and either saline, or one of the following organic nitrates: nitroglycerin (NTG, 0.5 mg kg-1), isosorbide dinitrate (ISDN), N-(3-nitratopivaloyl)-L-cysteine Et ester (SPM 3672), S-carboxyethyl-N-(3-nitratopivaloyl)-L-cysteine Et ester (SPM 5185), at 10 mg kg-1 each. After 20 min the animals were killed, blood vessels and organs were removed, and subsequently analyzed for spin-trapped NO by cryogenic ESR spectroscopy. In the saline-treated control group, NO remained below the detection limit in all vessels and organs. In contrast, all of the nitrates tested elicited measurable NO formation, which was higher in organs (liver, kidney, heart, lung, spleen) (up to 4.8 nmol g-1 20 min-1) than in the blood vessels (vena cava, mesenteric bed, femoral artery, aorta) (up to 0.7 nmol g-1 20 min-1). Classical organic nitrates (NTG, ISDN) formed NO preferentially in the mesenteric bed and the vena cava, while the SPM compds. elicited comparable NO formation in veins and arteries. Using a similar spin trapping technique, NO formation was assessed in vitro in phenylphrine-precontracted rabbit aortic rings. The maximal relaxation elicited by a first exposure (10 min) to NTG (0.3 to 10 μM) was pos. correlated (r = 0.8) with the net increase (NTG minus basal) of NO spin-trapped during a second exposure to the same concentration of NTG in the presence of DETC. Cytochrome P 450 purified from rabbit liver enhanced NO formation in a NADPH-dependent fashion from NTG, but

not from the other nitrates, as assessed by activation of purified soluble guanylyl cyclase. We conclude that the vessel selective action of different organic nitrates in vivo reflects differences in vascular NO formation. Thus, efficient preload reduction by classical organic nitrates can be accounted for by higher NO formation in venous capacitance as compared to arterial conductance and resistance vessels. In contrast, NO is released from cysteine-containing nitrates (SPMs) to a similar extent in arteries and veins, presumably independently of an organic nitrate-specific biotransformation. Limited tissue bioavailability of NTG and ISDN might account for low NO formation in the aorta, while true differences in biotransformation seem to account for differences in NO formation in the other vascular tissues.

IT **130432-17-6**, SPM 3672 **139146-66-0**, SPM 5185
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(specificity of different organic nitrates to elicit NO formation in vascular tissues and organs)

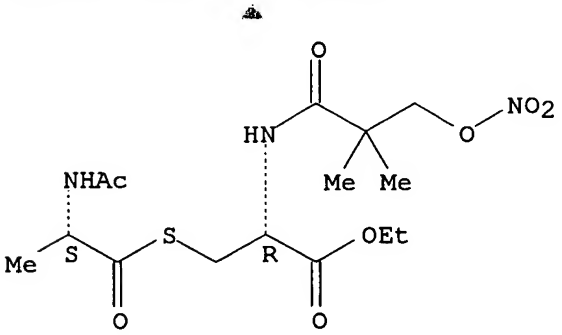
RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 16 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:828934 CAPLUS
DOCUMENT NUMBER: 123:275504
TITLE: The new NO donor SPM3672 increases cGMP and improves contraction in rat cardiomyocytes and

isolated heart

AUTHOR(S): Kojda, Georg; Brixius, Klara; Kottenberg, Karin; Nix, Petra; Schlueter, Klaus-Dieter; Piper, Hans Michael; Noack, Eike

CORPORATE SOURCE: Institut fuer Pharmakologie, Heinrich-Heine-Universitaet, Moorenstr. 5, Dusseldorf, 40225, Germany

SOURCE: European Journal of Pharmacology (1995), 284(3), 315-19
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

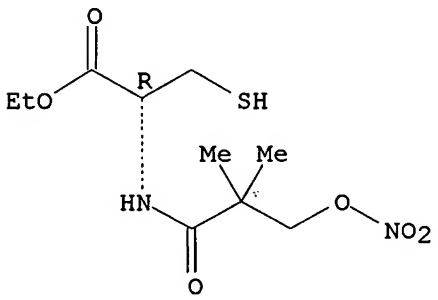
AB Recent evidence indicates that organic nitrate esters may directly affect heart muscle. In the present study the authors investigated the effects of the new organic nitrate ester, N-(3-nitratopivaloyl)-1-cysteine Et ester (SPM3672), on isolated adult rat ventricular myocytes and on Langendorff prepns. of spontaneously beating rat hearts perfused in a volume-constant manner. In cardiomyocytes SPM3672 (100 μM) induced a significant increase in the basal level of cGMP to 232% indicating its metabolism to nitric oxide. This was associated with an enhanced contractile response to elec. field stimulation (to 174%). In isolated hearts SPM3672 elicited a slight reduction of coronary perfusion pressure (-15%) and a significant increase in maximal left ventricular pressure (LVPmax), dp/dtmax and dp/dtmin amounting to 18%, 18% and 21%, resp. Oxygen consumption and heart rate remained constant Thus, SPM3672 improved the contractile response of cardiomyocytes and of isolated heart. This is probably due to the metabolism of SPM3672 to nitric oxide in ventricular cardiomyocytes.

IT **130432-17-6**, SPM3672
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(the new NO donor SPM3672 increases cGMP and improves contraction in rat cardiomyocytes and isolated heart)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 17 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

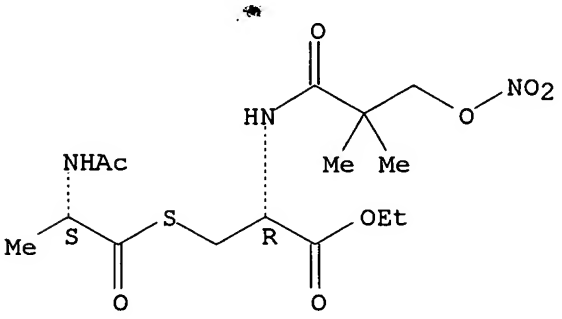
ACCESSION NUMBER: 1995:793930 CAPLUS

DOCUMENT NUMBER: 123:218065

TITLE: Development of nitrate tolerance in human arteries and veins: comparison of nitroglycerin and SPM 5185

AUTHOR(S): Arnet, Urs; Yang, Zhihong; Siebenmann, Robert; von Segesser, Ludwig K.; Turina, Marko; Stulz, Peter; Luscher, Thomas F.
CORPORATE SOURCE: Dep. of Research Lab. of Vascular Res., Univ. Hospitals, Zurich, Switz.
SOURCE: Journal of Cardiovascular Pharmacology (1995), 26(3), 401-6
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nitrate tolerance is a clin. problem in patients with coronary artery disease and heart failure. Human internal mammary arteries and saphenous veins obtained intraoperatively were suspended in organ chambers, and isometric tension was measured. In the artery, nitroglycerin elicited a potent relaxation, which was significantly diminished after prolonged incubation with nitroglycerin (10-6M, 1 h). In contrast, no tolerance occurred in saphenous vein under the same conditions. However, incubation with 10-5M nitroglycerin also developed tolerance. Compared to nitroglycerin, the new cysteine-containing mononitrate SPM 5185 exhibited a lower sensitivity but comparable maximal relaxation in arteries and veins. In nitroglycerin-tolerant arteries and veins, SPM 5185 caused relaxations similar to those under control conditions. Our results show that in isolated blood vessels, vascular nitrate tolerance occurs more readily in the mammary artery than in the saphenous vein. SPM 5185 seems to be less prone to the development of tolerance, which may be advantageous during chronic nitrate therapy.
IT **139146-66-0**, SPM 5185
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development of nitrate tolerance in human arteries and veins and comparison of nitroglycerin and SPM 5185)
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 18 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:777652 CAPLUS
DOCUMENT NUMBER: 123:199401
TITLE: Preparation of amino acid disulfide cardiovascular agents and vasodilators
INVENTOR(S): Sandrock, Klaus; Feelisch, Martin; Boekens, Hilmar

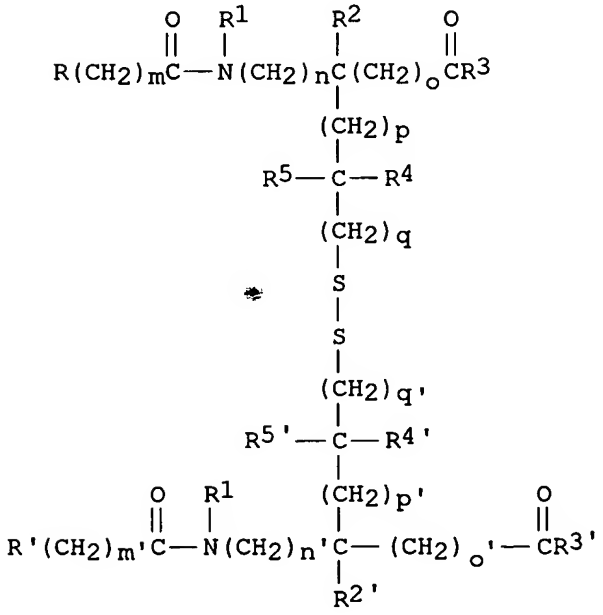
PATENT ASSIGNEE(S): Schwarz Pharma AG, Germany
SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4321306	A1	19950105	DE 1993-4321306	19930626
WO 9500477	A1	19950105	WO 1994-DE726	19940624
W: CA, CN, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 705244	A1	19960410	EP 1994-918734	19940624
EP 705244	B1	19981104		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1126466	A	19960710	CN 1994-192601	19940624
CN 1045594	B	19991013		
JP 08511777	T2	19961210	JP 1994-502335	19940624
AT 172963	E	19981115	AT 1994-918734	19940624
ES 2126122	T3	19990316	ES 1994-918734	19940624
CA 2165992	C	20000822	CA 1994-2165992	19940624
US 5661129	A	19970826	US 1995-557106	19951205
HK 1013283	A1	20000519	HK 1998-114613	19981222

PRIORITY APPLN. INFO.: DE 1993-4321306 A 19930626
WO 1994-DE726 W 19940624

OTHER SOURCE(S): MARPAT 123:199401

GI



I

Searcher : Shears 571-272-2528

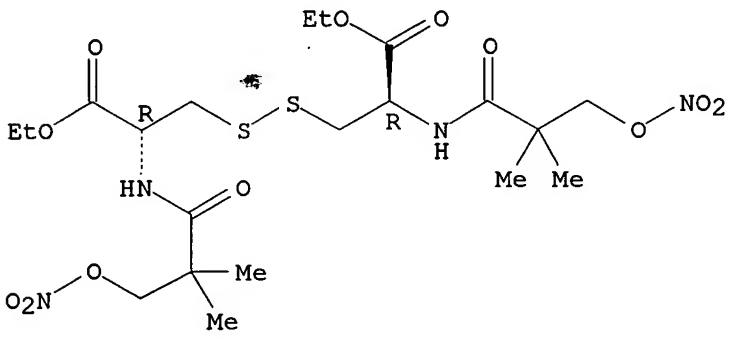
AB The title compds. [I; R, R' = (un)substituted nitratoalkyl, (un)substituted Ph; R1, R1', R4, R4', R5, R5' = H, lower alkyl; R2, R2' = H, (un)substituted lower alkyl, Ph, methoxyphenyl, etc.; R3, R3' = HO, lower alkenoxy, (un)substituted lower alkoxy, (un)substituted aryloxy, etc; m, m', n, n', p, p', q, q' = 0-10] [e.g., N,N'-di(3-nitratopivaloyl)-L-cystine di-Et ester (II)], useful as cardiovascular agents and vasodilators, are prepared and a I-containing formulation presented. II was prepared and demonstrated a EC50 for 50% dilation of excised rat aorta rings of 1.5 x 10-6 M.

IT **167370-45-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino acid disulfide cardiovascular agents and vasodilators)

RN 167370-45-8 CAPLUS

CN L-Cystine, N,N'-bis[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, diethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

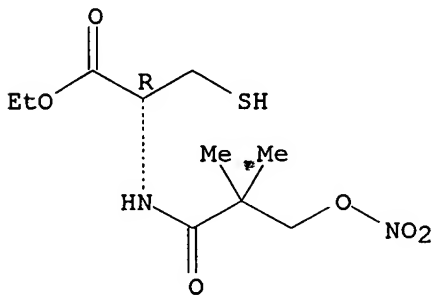


IT **130432-17-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of amino acid disulfide cardiovascular agents and vasodilators)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

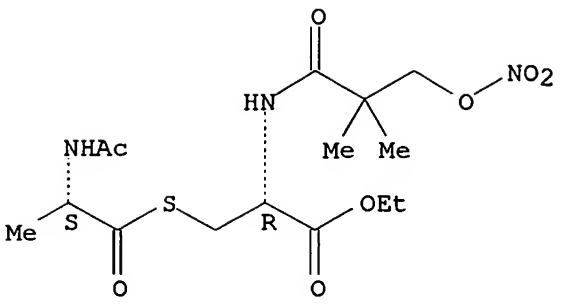


L5 ANSWER 19 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:719610 CAPLUS
DOCUMENT NUMBER: 123:132459
TITLE: Effect of nitric oxide donors on neointima formation and vascular reactivity in the collared carotid artery of rabbits
AUTHOR(S): De Mayer, Guido R. Y.; Bult, Hidde; Uestuenes, Levent; Kockx, Mark M.; Feelisch, Martin; Herman, Arnold G.
CORPORATE SOURCE: Division of Pharmacology, University of Antwerp, Antwerp, Belg.
SOURCE: Journal of Cardiovascular Pharmacology (1995), 26(2), 272-9
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Expts. investigated whether oral administration of the NO donors SPM-5185 (10 mg/kg twice daily) and molsidomine (10 mg/kg/day) can retard neointima formation and changes in vascular reactivity induced by a nonocclusive, soft silicone collar positioned around the left carotid artery of rabbits. The contralateral carotid artery was sham operated and served as a control. Drug and placebo (diet without drug) treatments were initiated 7 days before placement of the collar. At the end of the expts., 2 segments were cut from each collared and sham-treated artery, one for measurement of the cross-sectional area of intima and media and the other for isometric tension recording. Sham treatment did not result in intimal thickening in either group. In contrast, the intima/media ratio was considerably increased after 14 days of collar treatment, as a result of neointima formation. Intimal thickening was inhibited by SPM-5185, but not by molsidomine, which is a donor of both NO and superoxide anions. Neither collar nor NO donor treatment altered the area of the media. SPM-5185 did not alter the percentage of replicating smooth muscle cells in the media after collar treatment, as demonstrated by their immunoreactivity for proliferating cell nuclear antigen. Neointima formation was associated with a decreased sensitivity to acetylcholine (ACh), an increased sensitivity to 5-hydroxytryptamine (5-HT), and a decreased maximum force development in response to 5-HT and KCl. Despite the reduction of intimal thickening, SPM-5185 did not antagonize these collar-induced modifications in vascular reactivity, although a tendency toward normalization of the pD2 value of ACh in collared arteries was observed Moreover, SPM-5185 did not lead to cross-tolerance to the effects of nitroglycerin. Thus, development of a neointima can be inhibited by the NO donor SPM-5185.

IT **139146-66-0**, SPM 5185
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of nitric oxide donors on intima formation and vascular reactivity in carotid artery)
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



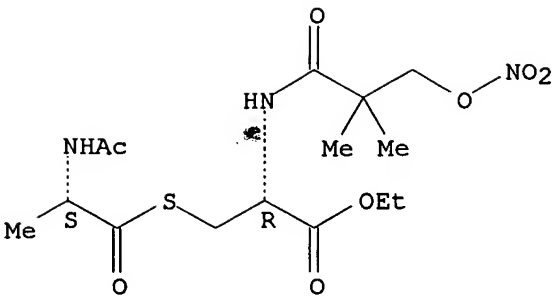
L5 ANSWER 20 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:706717 CAPLUS
DOCUMENT NUMBER: 123:132443
TITLE: In vivo effect of the cysteine-containing nitric oxide donor SPM-5185 on neo-intima formation in the collared carotid artery of the rabbit
AUTHOR(S): De Meyer, G. R. Y.; Bult, H.; Ustunes, L.; Kockx, M. M.; Van Den Bossche, R.; Zonnekeyn, L. L.; Feelisch, M.; Herman, A. G.
CORPORATE SOURCE: Division Pharmacology, University Antwerp, Antwerp, Belg.
SOURCE: Portland Press Proceedings (1994), 8(Biology of Nitric Oxide, 4), 284-6
CODEN: POPPEF; ISSN: 0966-4068
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oral treatment with the cysteine-containing NO donor SPM-5185 retarded the development of a neo-intima induced by the positioning of a silicone collar around the rabbit carotid artery. The reduction of neo-intima formation by SPM-5185 may be due to an inhibition of proliferation and/or migration of medial smooth muscle cells. Possible role for NO in the modulation of proliferation and/or migration of vascular smooth muscle is suggested.

IT **139146-66-0**, SPM-5185
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cysteine-containing nitric oxide donor SPM-5185 inhibition of neo-intima formation in collared carotid artery)

RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

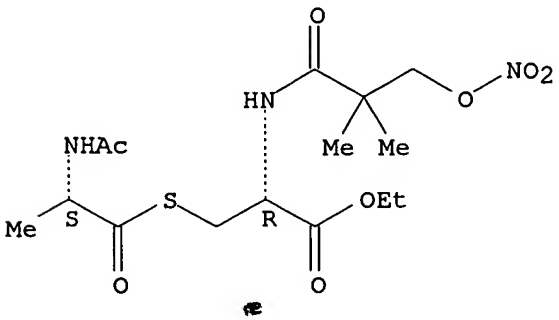


L5 ANSWER 21 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:706715 CAPLUS
DOCUMENT NUMBER: 123:132441
TITLE: New nitric oxide donor compounds are associated with reduced tolerance during long-term infusion in dogs
AUTHOR(S): Zanzinger, J.; Feelisch, M.; Bassenge, E.
CORPORATE SOURCE: Department Applied Physiology, University Freiburg, Freiburg/Br., 79104, Germany
SOURCE: Portland Press Proceedings (1994), 8(Biology of Nitric Oxide, 4), 275-9
CODEN: POPPEF; ISSN: 0966-4068
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Both SPM 4744 and SPM 5185 act as potent dilators of large coronary arteries which do not induce significant tolerance during 5-day administration in dogs. The advantageous pharmacol. properties of these new compds. may be related to a unique mechanism of NO release in vivo. The cysteine moiety of SPM 5185 improves the dilatory efficacy if this organic nitrate but is probably not a prerequisite for the maintenance of its dilatory capacity during chronic administration.

IT **139146-66-0**, SPM 5185
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(reduced tolerance of nitric oxide donors SPM 4744 and SPM 5185)
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

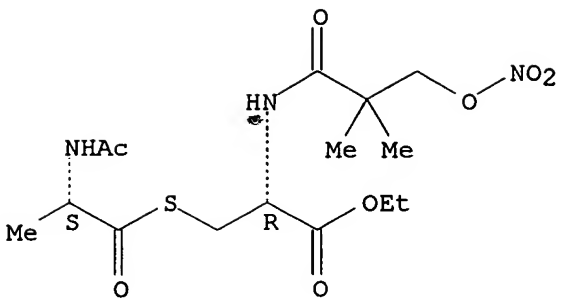


L5 ANSWER 22 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:91079 CAPLUS
DOCUMENT NUMBER: 122:28762
TITLE: Physiological concentrations of nitric oxide do not elicit an acute negative inotropic effect in unstimulated cardiac muscle
AUTHOR(S): Weyrich, Andrew S.; Ma, Xin-liang; Buerke, Michael; Murohara, Toyoaki; Armstead, Valerie E.; Lefer, Allan M.; Nicolas, Josep M.; Thomas, Andrew P.; Lefer, David J.; Vinten-Johansen, Jakob
CORPORATE SOURCE: Dep. Physiol., Jefferson Med. Coll., Philadelphia, PA, 19107, USA
SOURCE: Circulation Research (1994), 75(4), 692-700
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors examined the effect of several nitric oxide (NO) donors, authentic NO gas, and L-arginine in isolated cat and rat papillary muscles. The authors did not observe significant inotropic effects in response to any NO donor (i.e., SPM-5185, C87-3754, and S-nitroso-N-acetylpenicillamine [SNAP]) from 1 nmol/L to 100 μmol/L. Similarly, authentic NO, at concns. far in excess of those that maximally dilate the coronary vasculature (i.e., 500 nmol/L), also failed to exert a detectable inotropic effect in these prepns. However, in the presence of 5 μmol/L norepinephrine, 500 nmol/L NO exerted a 12 ± 3% decrease in isolated rat papillary muscle contractility ($P < .05$). Addition of L-arginine up to 25 mmol/L exerted no inotropic effects in isolated rat papillary muscles. However, a 50 mmol/L, L-arginine decreased contractile force by 21 ± 4% ($P < .01$). On further examination, the neg. inotropic effect of 50 mmol/L L-arginine appeared to be nonspecific, since the inactive stereoisomer, D-arginine, at 50 mmol/L exerted the same effect. Further studies in isolated adult rat cardiac myocytes elicited similar results, in that 50 mmol/L of L- and D-arginine equally decreased contraction amplitude and the underlying cytosolic calcium transient. Moreover, 500 nmol/L of the NO donor SPM-5185 only modestly decreased contraction amplitude or intracellular calcium in isolated rat cardiac myocytes. These results indicate that administration of physiol. concns. of exogenous NO does not acutely depress the inotropic state of the rat or cat heart to a physiol. significant extent. Only in the presence of high concns. of norepinephrine did NO exert a statistically significant neg. inotropic effect, and this effect was a modest one. These data demonstrate that physiol. levels of NO do not exert a major regulatory effect on cardiac contractility.

IT **139146-66-0**, SPM-5185
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(failure to elicit an acute neg. inotropic effect in unstimulated cardiac muscle as nitric oxide donor)
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 23 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:595361 CAPLUS
DOCUMENT NUMBER: 121:195361
TITLE: Beneficial effect of SPM-5185, a cysteine-containing nitric oxide donor, in rat carotid artery intimal injury
AUTHOR(S): Guo, Jin Ping; Milhoan, Kirk A.; Tuan, Rocky S.; Lefer, Allan M.
CORPORATE SOURCE: Department Physiology, Jefferson Medical College, Philadelphia, PA, 19107, USA
SOURCE: Circulation Research (1994), 75(1), 77-84
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We studied the effects of an organic nitric oxide (NO) donor SPM-5185 in a rat carotid artery intimal injury model. Seven days after injury, the two end segments of the injured carotid arteries were studied for endothelial release of NO, and the middle segments were used for histol. measurement of the intimal-to-medial (I/M) ratio and SEM of the luminal surface. The NO donor SPM-5185 or its non-NO-donating control compound SPM-5267 were infused i.v. at 30 μg/d. Full vasorelaxant responses of rat carotid arterial rings were obtained with the endothelium-dependent vasodilators acetylcholine (ACh), A23187, and the endothelium-independent vasodilator acidified NaNO2 in sham-operated control rings. Impaired relaxation occurred with 10 μmol/L ACh and 1 μmol/L A23187 in injured rings but not in rings infused with SPM-5185 for 7 days. Relaxation to 100 μmol/L acidified NaNO2 was not significantly different among any of the groups, indicating a normal vascular smooth muscle response after intimal injury. Morphometric anal. of injured carotid arteries given vehicle and SPM-5267 showed marked intimal thickening with an average I/M ratio of 0.78 ± 0.03 and 0.74 ± 0.05, resp. SPM-5185 markedly attenuated intimal thickening, resulting in an I/M ratio of 0.12 ± 0.03 ($P < .01$ from vehicle), representing an ≈82% inhibition of intimal thickening. SPM-5185 infusion resulted in accelerated regeneration of endothelial cells on the intimal surface at 7 days. SPM-5185 also markedly retarded the proliferation of cultured rat vascular smooth muscle cells at 7 days compared with SPM-5267 ($P < .01$). We conclude that a constant i.v. infusion of a subvasodilator dose of NO donor SPM-5185 significantly accelerates the functional recovery of the regenerating endothelium and also inhibits vascular smooth muscle cell proliferation, which contributes to myointimal thickening.

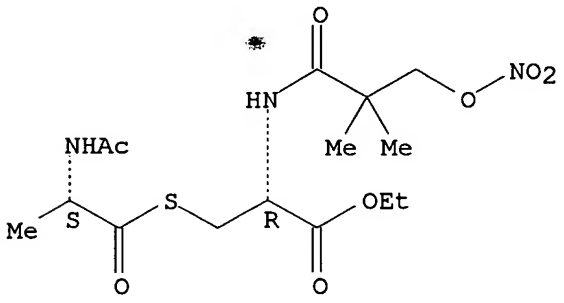
IT **139146-66-0**, SPM-5185
RL: BAC (Biological activity or effector, except adverse); BSU

(Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cysteine-containing nitric oxide donor SPM-5185 effect on carotid artery intimal injury)

RN 139146-66-0 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 24 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:558196 CAPLUS

DOCUMENT NUMBER: 121:158196

TITLE: Preparation of nitratopivaloylcysteine derivatives and related compounds as cardiovascular agents

INVENTOR(S): Sandrock, Klaus; Noack, Eike; Fritschi, Edgar; Kanzler, Ralf; Feelisch, Martin

PATENT ASSIGNEE(S): Schwarz Pharma AG, Germany

SOURCE: U.S., 8 pp. Cont.-in-part of U.S. Ser. No. 406,165, abandoned.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 5284872	A	19940208	US 1991-681876		19910405
DE 4011505	A1	19911024	DE 1990-4011505		19900410
DE 4011505	C2	19950112			
US 5428061	A	19950627	US 1993-116946		19930907
PRIORITY APPLN. INFO.:			US 1989-406165	B2	19890912
			DE 1990-4011505	A	19900410
			DE 1988-3831311	A	19880915
			US 1992-818502	B1	19920108

OTHER SOURCE(S): MARPAT 121:158196

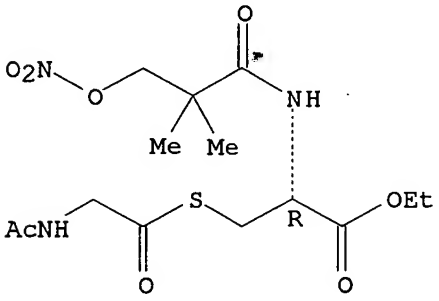
AB O2NOCH2CR1R2(CH2)mCONR3(CH2)nCR4R5(CH2)pCOR (R = OH, alkoxy; R1-R4 = H, alkyl; R5 = XSCOR6; X = alkylene, CMe2; R6 = specified amino acid residue; m, n, p = 0,1), were prepared Thus, N-acetylglycine and N-nitratopivaloylcysteine Et ester in CH2Cl2 were treated dropwise with DCC in CH2Cl2 at 5-10° to give N-nitratopivaloyl-S-(N-

acetylglycyl)cysteine Et ester (I). I and other title compds. were more potent than glycerol trinitrate in reducing arterial and central venous pressure in vivo in beagle dogs. A tablet formulation containing I is given. Title compds. released NO spontaneously at about the same rate as isosorbide dinitrate.

IT **139146-65-9P 139146-66-0P 139146-67-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as cardiovascular agent)

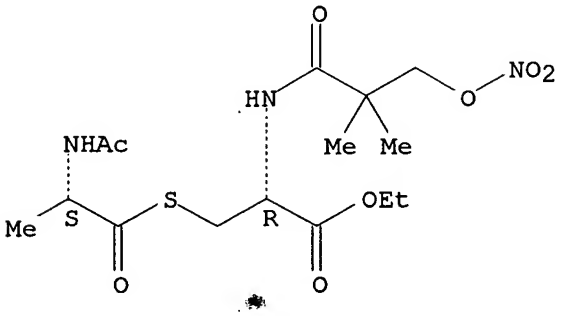
RN 139146-65-9 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetylglycine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



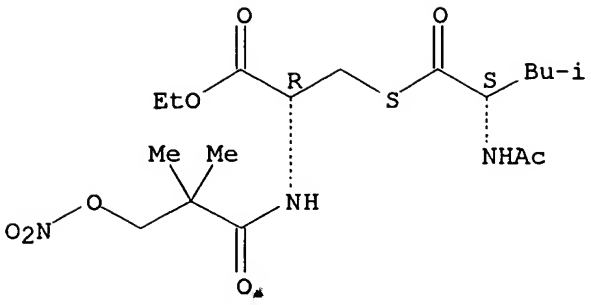
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



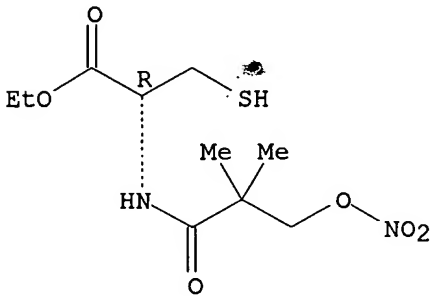
RN 139146-67-1 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-leucine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **130432-17-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of cardiovascular agent)
RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 25 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:449826 CAPLUS
DOCUMENT NUMBER: 121:49826
TITLE: Nitrovasodilator-induced relaxation and tolerance development in porcine vena cordis magna: dependence on intact endothelium
AUTHOR(S): Kojda, Georg; Beck, Jan Klaus; Meyer, Wilfried; Noack, Eike
CORPORATE SOURCE: Inst. Pharmakol., Heinrich-Heine Univ., Duesseldorf, D-40001, Germany
SOURCE: Br. J. Pharmacol. (1994), 112(2), 533-40
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Isolated segments of porcine vena cordis magna exhibited a reproducible contractile activity upon addition of PGF2α or KCl, and this was independent of the presence of intact endothelium. Substance P elicited strictly endothelium-dependent relaxations. S-nitroso-N-acetyl-DL-penicillamine (SNAP), a compound that spontaneously liberates NO, concentration-dependently relaxed PGF2α-precontracted venous segments. Tolerance induction (incubation with 100 μM SNAP for 30 min) within the same segments resulted in a 3-fold attenuation of this effect, which was not further reduced after addnl. preincubation with glyceryl trinitrate (GTN).

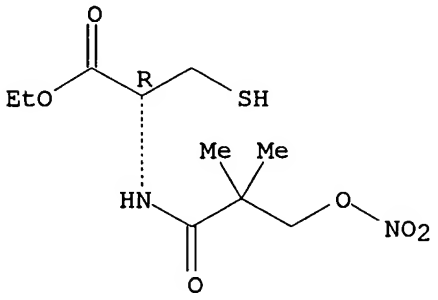
Removal of endothelium or the presence of Nω-nitro-L-arginine Me ester (L-NAME) improved the potency of SNAP before and after tolerance induction. Concentration-dependent relaxations induced by GTN in nontolerant veins were similar in the presence and absence of endothelium but were much more reduced in tolerant endothelium-denuded than in intact segments. In contrast, the presence of L-NAME improved GTN activity solely in nontolerant veins, which, therefore, also resulted in a more pronounced attenuation of activity due to tolerance induction. Preincubation of intact veins with SNAP also reduced GTN activity but to a lesser extent. The more delayed-acting but much longer-acting (and compared to GTN somewhat weaker-acting) new nitrovasodilator N-(3-nitratopivaloyl)-l-cysteine Et ester (SPM 3672) was more potent in denuded than intact nontolerant venous segments. Induction of tolerance by GTN resulted in a 2-old-attenuation of the potency of SPM 3672. This effect was increased to 15-fold in denuded veins but solely due to the enhanced potency of SPM 3672 caused by removal of endothelium. These data demonstrate that the intact endothelium of porcine vena cordis magna attenuates the relaxant potency of nitrovasodilators but also probably participates in vascular bioactivation of GTN. This reduced potency may be due to endogenous production of NO, which may affect the soluble guanylate cyclase/cyclic GMP system or inhibit nitrate bioactivation pathways.

IT **130432-17-6,** SPM 3672
RL: BIOL (Biological study)
(vein relaxation by and tolerance to, endothelium dependence of)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 26 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:400253 CAPLUS

DOCUMENT NUMBER: 121:253

TITLE: Novel organic nitrates are potent dilators of large coronary arteries with reduced development of tolerance during long-term infusion in dogs: role of the sulfhydryl moiety

AUTHOR(S): Zanzinger, Johannes; Feelisch, Martin; Bassenge, Eberhard

CORPORATE SOURCE: Dep. Appl. Physiol., Univ. Freiburg, Freiburg, Germany

SOURCE: Journal of Cardiovascular Pharmacology (1994), 23(5), 772-8
CODEN: JCPCDT; ISSN: 0160-2446

DOCUMENT TYPE: Journal
LANGUAGE: English

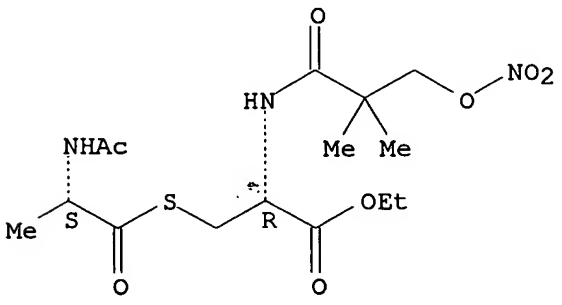
AB The vasodilator action of organic nitrates can be severely impaired by induction of drug tolerance. A critical depletion of sulfhydryl groups has been proposed to play a key role in impairment of the biotransformation of organic nitrates to nitric oxide (NO). The authors studied the effects of the new cysteine-containing nitrate SPM-5185 and the corresponding cysteine-free compound SPM-4744 on hemodynamics and large coronary artery dilation in chronically instrumented conscious dogs. Both nitrates caused dose-dependent increases of the diameter of the left circumflex artery (LCX); the cysteine-containing compound SPM-5185 however, caused such increases at ≤30-fold lower doses as compared with SPM-4744. Coinfusion of the cysteine-containing analog of SPM-5185 lacking the nitrate group (SPM-5267) did not alter the dose-response relationship to SPM-4744. Continuous infusion of SPM-5185 (4 μg/kg/min, n = 6) and SPM-4744 (2.7 μg/kg/min, n = 5) elicited LCX diameter increases of 0.24 ± 0.06 and 0.17 u 0.07 mm, resp., representing 60-70% of maximal dilator capacity. In contrast to classic organic nitrates, both SPM-5185 and SPM-4744 caused LCX diameter to decrease only slightly during 5-day infusions. Both compds. elicited sustained dilation even at day 5 ($p \leq 0.05$). SPM-5185 caused an initial decrease in mean arterial pressure (MAP) and evoked sustained increases in heart rate (HR), whereas SPM-4744 had no significant peripheral effects. On withdrawal of SPM-5185, LCX diameter was decreased below pretreatment values for several hours. The dose-response relationship was not altered significantly by chronic administration of either nitrate after 5 days of infusion nor 1 day after discontinuation of the infusion, demonstrating preservation of pharmacol. efficacy. SPM-5185 and SPM-4744 are both effective vasodilators that dilate large coronary arteries without rapid development of drug tolerance. The cysteine moiety probably is not a prerequisite for prevention of tolerance at the level of large coronary arteries but may improve pharmacol. properties of nitrate compds.

IT **139146-66-0**, SPM 5185
RL: BIOL (Biological study)
(as potent coronary vasodilator with reduced development of tolerance during long-term infusion, sulfhydryl moiety role in)

RN 139146-66-0 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

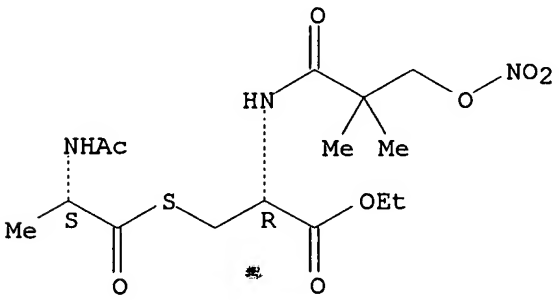
Absolute stereochemistry.



L5 ANSWER 27 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:235711 CAPLUS

DOCUMENT NUMBER: 120:235711
TITLE: Myocardial and endothelial protective effects of nitric oxide donors in feline myocardial ischemia and reperfusion
AUTHOR(S): Siegfried, Martin R.
CORPORATE SOURCE: Thomas Jefferson Univ., Philadelphia, PA, USA
SOURCE: (1993) 146 pp. Avail.: Univ. Microfilms Int., Order No. DA9324565
From: Diss. Abstr. Int. B 1993, 54(5), 2390
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT **139146-66-0**, SPM 5185
RL: BIOL (Biological study)
(in endothelium and heart protection after ischemia/reperfusion)
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 28 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:182729 CAPLUS
DOCUMENT NUMBER: 120:182729
TITLE: Antineutrophil and myocardial protecting actions of a novel nitric oxide donor after acute myocardial ischemia and reperfusion in dogs
AUTHOR(S): Lefer, David J.; Nakanishi, Katsuhiko; Johnston, William E.; Vinten-Johansen, Jakob
CORPORATE SOURCE: Bowman Gray Sch. Med., Wake Forest Univ., Winston-Salem, NC, 27157, USA
SOURCE: Circulation (1993), 88(5, Pt. 1), 2337-50
CODEN: CIRCAZ; ISSN: 0009-7322
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It has recently been demonstrated that myocardial ischemia and reperfusion results in a marked decrease in the release of nitric oxide (NO) by the coronary endothelium. NO may possess cardioprotective properties, possibly related to inhibition of neutrophil-related activities. The authors tested the hypothesis that a cysteine-containing nitric oxide donor compound, SPM-5185 [O2NOCH2CMe2CONHCH(CO2Et)CH2SCOCHMeNHAc], would reduce infarct size and inhibit neutrophil-related activities (adherence to coronary vascular endothelium, accumulation). SPM-5185 reduces myocardial necrosis and neutrophil accumulation in an acute model of canine myocardial ischemia and reperfusion. This reduction in myocardial cell

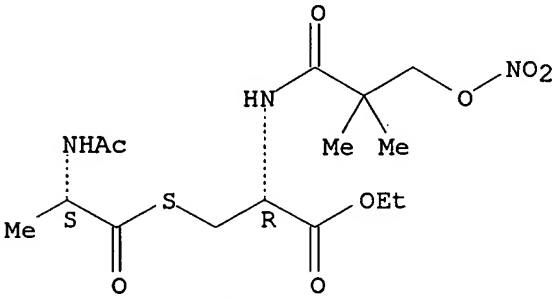
injury may be partially related to the inhibitory actions of this novel NO donor on neutrophil adherence to the coronary endothelium.

IT **139146-66-0**, SPM 5185
RL: PROC (Process)
(antineutrophil and myocardial protecting actions of, after acute myocardial ischemia and reperfusion)

RN 139146-66-0 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 29 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:95218 CAPLUS

DOCUMENT NUMBER: 120:95218

TITLE: Influence of endothelium and nitrovasodilators on free thiols and disulfides in porcine coronary smooth muscle

AUTHOR(S): Kojda, Georg; Meyer, Wilfried; Noack, Eike

CORPORATE SOURCE: Inst. Pharmackol., Heinrich-Heine Univ., Duesseldorf, D-40001, Germany

SOURCE: European Journal of Pharmacology (1993), 250(3), 385-94
CODEN: EJPHAZ; ISSN: 0014-2999

DOCUMENT TYPE: Journal

LANGUAGE: English

AB It is hypothesised that the well known development of tolerance to the vasodilating action of organic nitrates is contributed by intracellular depletion of free thiols occurring during repeated treatment with these drugs. Therefore, ring segments of porcine coronary arteries with and without endothelium were treated for 30 min with either vehicle or 100 μM of isosorbide-5-mononitrate, glyceryl trinitrate, S-nitroso-N-acetyl-D,L-penicillamine or N-(3-nitratopivaloyl)-l-cysteineethylester (SPM 3672), and the content of histochem. stained free thiols (-SH) and disulfides (S-S-) was measured densitometrically in single smooth muscle cells. In the presence of endothelium the content of -SH in smooth muscle cells of controls (n = 8) gave an extinction of 0.127 ± 0.013 in the intima and 0.120 ± 0.010 in the media. The corresponding values for S-S- were 0.684 ± 0.084 and 0.535 ± 0.120 (n = 8). Removal of endothelium reduced S-S- to 82.1 ± 7.0% and increased -SH to 126.7 ± 6.7%. Treatment with all nitrates reduced -SH in intact artery segments to a similar degree, ranging between 54.0 ± 4.4 and 68.7 ± .47% (n = 8-10). In contrast, S-S- content was less affected and reached values between 70.6 ± 2.8 and 91.6 ± 6.0% (n = 8-9). As evaluated by tension studies, tolerance developed for glycerol trinitrate and

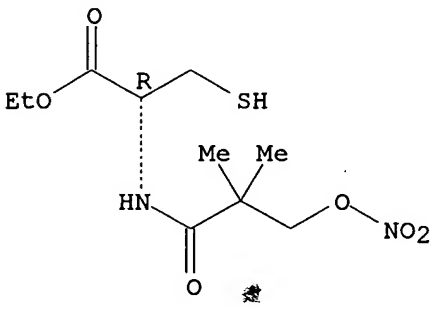
isosorbide-5-mononitrate but not for S-nitroso-N-acetyl-D,L-penicillamine. Induction of tolerance with glycerol trinitrate (0.1 mM) produced a significantly more pronounced attenuation in activity of isosorbide-5-mononitrate than tolerance induction with isosorbide-5-mononitrate (1 mM). In contrast, the potency of SPM 3672 was not reduced in glycerol trinitrate-tolerant arteries. The authors conclude that, in porcine coronary arteries, an intact endothelium modifies intracellular thiols and disulfides. In addition, nitrate tolerance is associated with, but probably not caused by, thiol depletion.

IT **130432-17-6**, SPM 3672
RL: BIOL (Biological study)
(vasodilation by, tolerance to, thiol and disulfide depletion in endothelium in)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 30 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:350 CAPLUS

DOCUMENT NUMBER: 120:350

TITLE: Endothelial and myocardial cell protection by a cysteine-containing nitric oxide donor after myocardial ischemia and reperfusion

AUTHOR(S): Lefer, David J.; Nakanishi, Katsuhiko; Vinten-Johansen, Jakob

CORPORATE SOURCE: Dep. Cardiothoracic Surg., Bowman Gray Sch. Med., Winston-Salem, NC, 27157-1096, USA

SOURCE: Journal of Cardiovascular Pharmacology (1993), 22(Suppl. 7), S34-S43
CODEN: JCPCDT; ISSN: 0160-2446

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The cardioprotective actions of SPM-5185, a novel cysteine-containing nitric oxide (NO) donor, were investigated in two models of myocardial ischemia-reperfusion (MI-R) injury. In the first study, dogs were subjected to 60 min of left anterior descending (LAD) coronary artery occlusion followed by 270 min of reperfusion. During reperfusion, animals were randomly assigned to receive intracoronary SPM-5185 (500 nM) or the NO-deficient analog of SPM-5185, SPM-5267 (500 nM). Transmural myocardial blood flow to the ischemic zone was not different between the SPM-5185 group of dogs and the SPM-5267 group. Similarly, the area of left ventricular myocardium placed at risk by LAD coronary artery occlusion was equivalent in dogs receiving SPM-5185

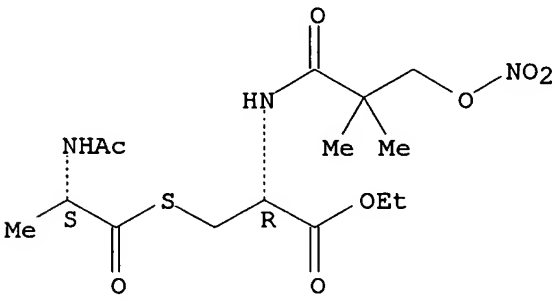
and SPM-5267. However, the necrotic area, expressed as a percentage of the area at risk, was reduced by 70% in the SPM-5185-treated dogs. Furthermore, cardiac myeloperoxidase activity indicated that fewer neutrophils accumulated in the necrotic zone of the SPM-5185-treated dogs. In the second study, dogs were subjected to 30 min of global myocardial ischemia followed by 1 h of cardioplegic arrest and 1 h of reperfusion. SPM-5185 (10 μM) added to the blood cardioplegia solution resulted in a 95% postischemic recovery of contractile function compared with 36% in vehicle-treated dogs. Addnl., SPM-5185 treatment completely preserved coronary arterial vasorelaxation to acetylcholine after ischemia and reperfusion and resulted in a 62% reduction in cardiac tissue myeloperoxidase activity. The authors conclude that (a) SPM-5185 exerts significant cardioprotection from MI-R injury after regional or global ischemia, and (b) this cardioprotection appears to be related to the inhibition of neutrophil-mediated injury.

IT **139146-66-0**, SPM 5185
RL: BIOL (Biological study)
(heart ischemia-reperfusion injury prevention by, nitric oxide and neutrophil in)

RN 139146-66-0 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 31 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:508736 CAPLUS

DOCUMENT NUMBER: 119:108736

TITLE: Nitric oxide liberating, soluble guanylate cyclase stimulating and vasorelaxing properties of the new nitrate-compound SPM 3672

AUTHOR(S): Kojda, Georg; Noack, Eike

CORPORATE SOURCE: Inst. Pharmakol., Heinrich-Heine Univ., Duesseldorf, D-4000/1, Germany

SOURCE: Journal of Cardiovascular Pharmacology (1993), 22(1), 103-11
CODEN: JCPCDT; ISSN: 0160-2446

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Development of tolerance as a consequence of organic nitrate therapy such as that which occurs with glyceryl trinitrate (GTN) appears to be associated with a depletion of free thiols in vascular smooth muscle. In this study, the authors investigated N-[3-nitratopivaloyl]-L-cysteine ethyl ester (SPM 3672), a new compound containing a nitrate and a thiol moiety, in direct comparison with GTN. Liberation of nitric oxide (NO) from GTN and SPM 3672 measured in vitro was rather low and was

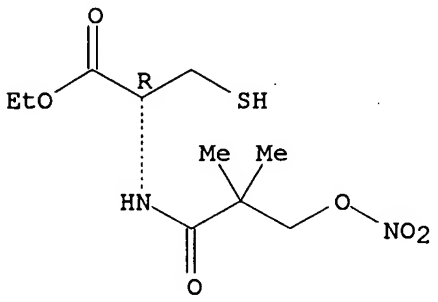
markedly potentiated by addition of cysteine only in the case of GTN. Pronounced activation of a partially purified human soluble guanylate cyclase (sGC) by GTN was observed only after addition of cysteine, whereas a comparative activation of SPM 3672 occurred with and without addition of this thiol. In contrast, SPM 4946 (N-[3-hydroxypivaloyl]-L-cysteine ethyl ester), a derivative of SPM 3672 lacking the nitrate-ester moiety, did not activate sGC. Activation of sGC by GTN and SPM 3672 was nearly abolished by oxyHb. Incubation of isolated porcine coronary artery rings with GTN or SPM 3672 resulted in a similar increase in vascular cyclic GMP levels. In rat aorta, GTN was a more potent vasorelaxant than SPM 3672 and produced a greater degree of tolerance. Vasorelaxation induced by GTN occurred with rapid onset and was brief, whereas SPM 3672 produced long-lasting relaxation with a more delayed onset. This kinetic pattern was confirmed in porcine coronary arteries, in which both nitrates exhibited marked relaxation, with GTN being slightly more potent than SPM 3672. Preincubation with 100 μM GTN produced a pronounced tolerance to GTN but not to SPM 3672, indicating the absence of cross-tolerance. SPM 3672, a nitrovasodilator with a long-lasting action and a comparably low tendency to induce tolerance may therefore serve as a therapeutic alternative to current nitrovasodilators in the future.

IT **130432-17-6**, SPM 3672
RL: BIOL (Biological study)
(vasodilation by, nitric oxide liberation and guanylate cyclase stimulation in)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 32 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:508380 CAPLUS

DOCUMENT NUMBER: 119:108380

TITLE: Sulfhydryl-containing organic nitrates. A new class of nitrovasodilator with direct nitric oxide-donating properties

AUTHOR(S): Noack, E. A.; Sandrock, K.; Huetter, J.

CORPORATE SOURCE: Inst. Pharmacol., Heinrich-Heine-Univ., Duesseldorf, D-4000, Germany

SOURCE: Biol. Nitric Oxide, Proc. Int. Meet., 2nd (1992), Meeting Date 1991, Volume 1, 135-9. Editor(s): Moncada, Salvador. Portland Press: London, UK. CODEN: 59AFA7

DOCUMENT TYPE: Conference

LANGUAGE: English

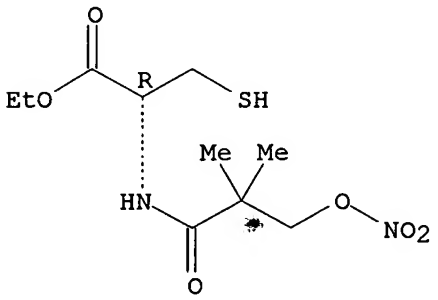
AB A new class of nitric oxide (NO)-containing compds., intramolecularly carrying their own cysteine moiety, independent of exogenous thiol-containing compds. or an enzymic stimulus for NO generation was developed so that NO liberation takes place spontaneously. N-nitratocarboxylic acid-cysteine Et esters are such potent NO-liberating compds. Structure-activity relations are discussed.

IT **130432-17-6**
RL: BIOL (Biological study)
(vasodilation by, nitric oxide-donating properties in)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 33 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:420174 CAPLUS

DOCUMENT NUMBER: 119:20174

TITLE: Anti-neutrophil and myocardial protecting actions of SPM-5185, a novel nitric oxide donor, following acute myocardial ischemia and reperfusion in dogs

AUTHOR(S): Lefer, D. J.; Nakanishi, K.; Johnston, W. E.; Feelisch, M.; Vinten-Johansen, J.

CORPORATE SOURCE: Dep. Cardiothoracic Surg., Bowman Gray Sch. Med., Winston-Salem, NC, 27103, USA

SOURCE: Biol. Nitric Oxide, Proc. Int. Meet., 2nd (1992), Meeting Date 1991, Volume 1, 188-90. Editor(s): Moncada, Salvador. Portland Press: London, UK. CODEN: 59AFA7

DOCUMENT TYPE: Conference

LANGUAGE: English

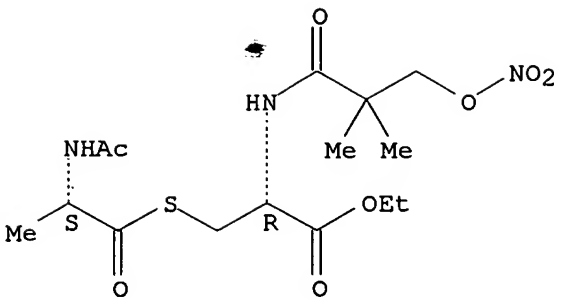
AB SPM-5185 (I) protected myocardium against ischemia-reperfusion injury. This cardioprotective action of I was partly attributed to the anti-neutrophil action of the nitric oxide donor.

IT **139146-66-0**, SPM 5185
RL: BIOL (Biological study)
(in protection against myocardial injury from ischemia and reperfusion, antineutrophil activity in relation to)

RN 139146-66-0 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

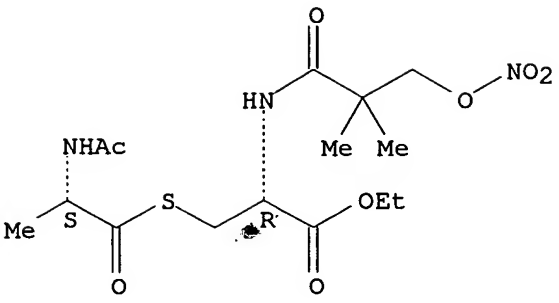


L5 ANSWER 34 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:420171 CAPLUS
DOCUMENT NUMBER: 119:20171
TITLE: Cytoprotective actions of nitric oxide donors in ischemia-reperfusion injury
AUTHOR(S): Lefer, A. M.
CORPORATE SOURCE: Jefferson Med. Coll., Thomas Jefferson Univ., Philadelphia, PA, 19107, USA
SOURCE: Biol. Nitric Oxide, Proc. Int. Meet., 2nd (1992), Meeting Date 1991, Volume 1, 55-6. Editor(s): Moncada, Salvador. Portland Press: London, UK. CODEN: 59AFA7
DOCUMENT TYPE: Conference
LANGUAGE: English

AB In addition to its vasorelaxing effect on vascular smooth muscle, nitric oxide (NO) has been shown to exert several other effects including (a) inhibition of platelet aggregation, (b) quenching of superoxide radicals, and (c) inhibition of polymorphonuclear leukocyte (PMN) activation. These latter cytoprotective effects were thought to be potentially useful activities in ischemia-reperfusion injury where thrombosis may be involved in the initial ischemic events and where PMNs and superoxide radicals may play a key role in propagating reperfusion injury. These considerations prompted the study of several NO donors (i.e. organic NO generators) and NO itself in a feline model of myocardial ischemia and reperfusion. All of the NO donors employed (i.e. acidified NaNO2, C87-3786 and SPM-5185) and authentic NO gas significantly reduced infarct size in this feline model of myocardial ischemia and reperfusion.

IT **139146-66-0**, SPM 5185
RL: BIOL (Biological study)
(in protection against heart ischemia-reperfusion injury, nitric oxide donor activity in relation to)
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



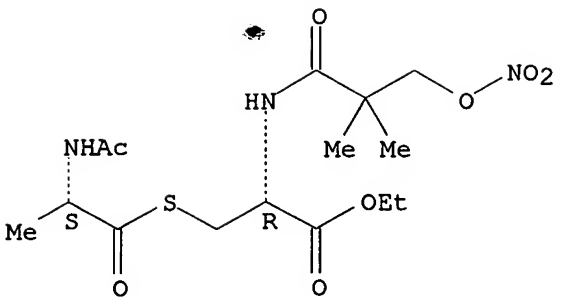
L5 ANSWER 35 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:16031 CAPLUS
DOCUMENT NUMBER: 118:16031
TITLE: Beneficial effects of SPM-5185, a cysteine-containing nitric oxide donor in myocardial ischemia-reperfusion
AUTHOR(S): Siegfried, Martin R.; Carey, Christopher; Ma, Xin Liang; Lefer, Allan M.
CORPORATE SOURCE: Jefferson Med. Coll., Thomas Jefferson Univ., Philadelphia, PA, 19107, USA
SOURCE: American Journal of Physiology (1992), 263(3, Pt. 2), H771-H777
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB I.v. administration of SPM-5185 [N-nitratopivaloyl-S-(N'-acetylalanyl)-cysteine Et ester], a cysteine-containing nitric oxide (NO) donor, on SPM-5267 [pivaloyl-S-(N'-acetylalanyl)-cysteine Et ester], an analog of SPM-5185 that lacks the NO moiety, was studied in a feline myocardial ischemia-reperfusion model. Administration of SPM-5185 (1 mg/kg), followed by a 2-mg·kg-1·h-1 infusion starting 10 min before reperfusion, resulted in significant protection 4.5 h post reperfusion. In the myocardial ischemia (MI) + SPM-5267 group, 38 ± 4% of the area at risk was necrotic, whereas the necrotic area/area at risk was only 7 ± 2% in the MI + SPM-5185 group ($P < 0.01$). Moreover, SPM-5185 treatment markedly attenuated the endothelial dysfunction observed in the left anterior descending coronary artery after reperfusion by 50%. These beneficial effects occurred despite the absence of a significant change in myocardial oxygen demand, as measured by the pressure-rate index. In vitro expts. demonstrated that SMP-5185, but not SPM-5267, decreased adherence of neutrophils to the coronary vascular endothelium and decreased production of superoxide radicals. Therefore, a likely mechanism of the observed cardioprotection by SPM-5185 involves attenuation of polymorphonuclear leukocyte-induced endothelial dysfunction.

IT **139146-66-0**
RL: BIOL (Biological study)
(attenuation of heart ischemia-reperfusion damage by, as nitric oxide donor, polymorphonuclear leukocyte-induced endothelial dysfunction inhibition in)

RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 36 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:106790 CAPLUS
DOCUMENT NUMBER: 116:106790
TITLE: Preparation of N-nitratopivaloyl-S-acylcysteines and related compounds as cardiovascular agents
INVENTOR(S): Sandrock, Klaus; Noack, Eike; Fritschi, Edgar; Kanzler, Ralf; Feelisch, Martin
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

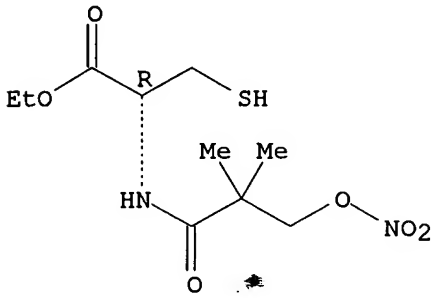
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 451760	A1	19911016	EP 1991-105540	19910408
EP 451760	B1	19950913		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DE 4011505	A1	19911024	DE 1990-4011505	19900410
DE 4011505	C2	19950112		
PL 167089	B1	19950731	PL 1991-289788	19910408
ES 2079506	T3	19960116	ES 1991-105540	19910408
FI 9101703	A	19911011	FI 1991-1703	19910409
FI 111074	B1	20030530		
HU 57707	A2	19911230	HU 1991-1143	19910409
HU 218202	B	20000628		
JP 05178804	A2	19930720	JP 1991-76186	19910409
JP 2848979	B2	19990120		
RU 2017748	C1	19940815	RU 1991-4895074	19910409
CZ 279744	B6	19950614	CZ 1991-984	19910409
SK 278385	B6	19970205	SK 1991-984	19910409
PRIORITY APPLN. INFO.:			DE 1990-4011505 A	19900410

OTHER SOURCE(S): MARPAT 116:106790
AB O2NOCH2CR1R2(CH2)mCONR3(CH2)nCR4R5(CH2)oCOR [R = OH, alkoxy, alkenyloxy, aminoalkoxy, (substituted) aralkoxy, aryloxy, amino, amino acid residue; R1 = H, (substituted) alkyl; R2, R3 = H, alkyl; R4 = R2, Ph, methoxyphenyl, phenylalkyl, hydroxyalkyl, acylaminoalkyl, mercaptoalkyl, etc.; R5 = acylthioalkyl; or RR4 = ester or amide bond; R3R4 = (substituted) (S-interrupted) alkylene, alkenylene; m, n, o = 0-10], were prepared Thus, N-acetylglycine and N-nitratopivaolylcysteine Et ester were condensed in CH2Cl2 using DCC to give N-nitratopivaloyl-S-(N-acetylglycyl)cysteine Et ester (I). I at

1.7 μmol/kg i.v. in dogs reduced systolic arterial pressure by 23 mmHg and central venous pressure by 46 mm Hg. Tablets were prepared containing I.

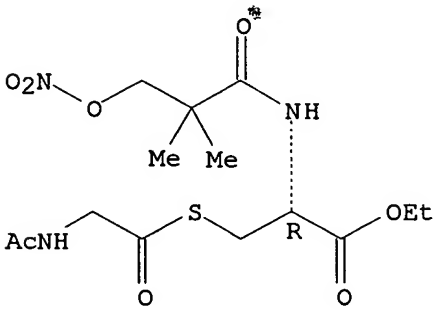
IT **130432-17-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(S-acylation of, in preparation of cardiovascular agent)
RN 130432-17-6 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



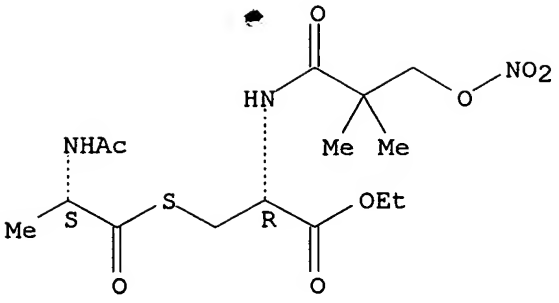
IT **139146-65-9P 139146-66-0P 139146-67-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as cardiovascular agent)
RN 139146-65-9 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetylglycine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



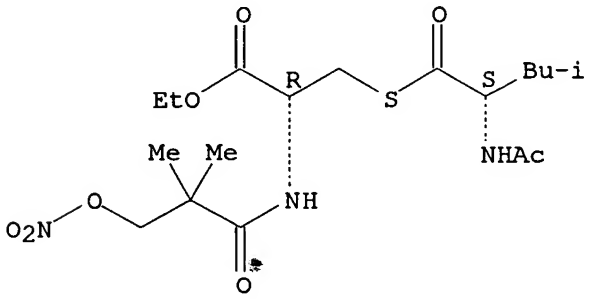
RN 139146-66-0 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139146-67-1 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, ester with N-acetyl-L-leucine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 37 OF 37 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:612672 CAPLUS
DOCUMENT NUMBER: 113:212672
TITLE: Preparation of N-(hydroxyalkanoyl)-L-methione or -cysteine nitrate derivatives for treatment of heart disease
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Jpn. Kokai Tokkyo Koho, 18 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 02091054	A2	19900330	JP 1989-192477	19890725
JP 2628756	B2	19970709		
EP 362575	A1	19900411	EP 1989-116700	19890909
EP 362575	B1	19950412		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 121077	E	19950415	AT 1989-116700	19890909
ES 2073418	T3	19950816	ES 1989-116700	19890909
DK 8904529	A	19900316	DK 1989-4529	19890914
FI 8904350	A	19900316	FI 1989-4350	19890914
FI 95569	B	19951115		
FI 95569	C	19960226		

HU 51229	A2	19900428	HU 1989-4831	19890914
HU 209716	B	19941028		
PL 163343	B1	19940331	PL 1989-281420	19890914
CZ 284586	B6	19990113	CZ 1989-5303	19890914
SK 280513	B6	20000313	SK 1989-5303	19890914
US 5428061	A	19950627	US 1993-116946	19930907
PRIORITY APPLN. INFO.:			DE 1988-3831311	A 19880915
			US 1989-406165	B2 19890912
			US 1992-818502	B1 19920108

OTHER SOURCE(S): MARPAT 113:212672

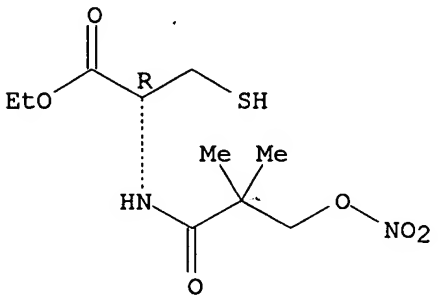
AB O2NOCR1R2(CH2)mCONR3(CH2)nCR4R5(CH2)oCOR [I; R = OH, alkoxy, alkenoxy, dialkylaminoalkoxy, acylaminoalkoxy, acyloxyalkoxy, aryloxy or aralkyloxy optionally substituted by Me, halo, MeO, or amino acid residue bonded through hydroxyamino, (un)substituted amino, or a peptide bond; R1 = H, (un)substituted alkyl; R2, R3 = H, alkyl; R4 = H, alkyl, Ph, methoxyphenyl, phenylalkyl, etc.; R5 = alkylthio, acylthio, SCO2R, SC(O)NHR, etc.; or RR5 = thiolactone; or RR4 = ester or amide bond; or R3R4 = C2-4 alkylene, C2-3 alkylene containing S, C3-4 alkylene containing a double bond and substituted with OH, alkoxy, or (di)alkyl; m, n, o = 0-10] which inhibit or diminish the nitrate tolerance of heart tissue and are useful as vasodilators and for the treatment of hypertensive heart failure, are prepared Thus, H-Met-OEt was condensed with O2NOCH2CMe2CO2H (preparation given) in the presence of DCC in CH2Cl2 to give 78.0% O2NOCH2CHC2CO-Met-OEt (II). A total of 42 I were prepared and II and O2NOCH2CMe2-Cyx-OEt was comparable to isosorbit 5-nitrate in effect on various heart parameters, e.g., blood pressure and heart rate,in adult dogs.

IT **130432-17-6P 130432-18-7P 130432-19-8P**
130432-20-1P 130432-21-2P 130432-22-3P
130432-23-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as vasodilator for treatment of heart disease)

RN 130432-17-6 CAPLUS

CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester (9CI) (CA INDEX NAME)

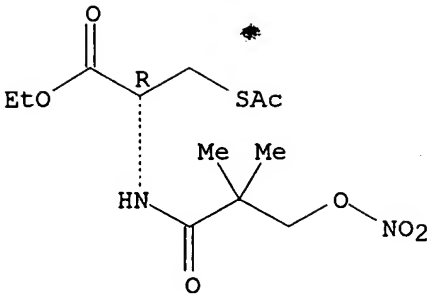
Absolute stereochemistry.



RN 130432-18-7 CAPLUS

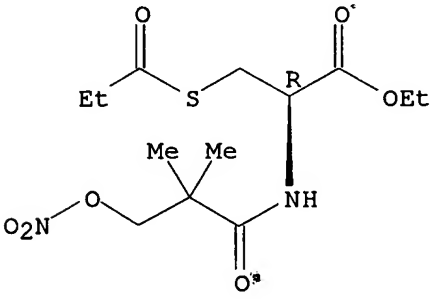
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, acetate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



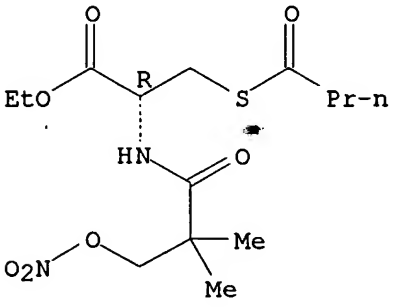
RN 130432-19-8 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, propanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



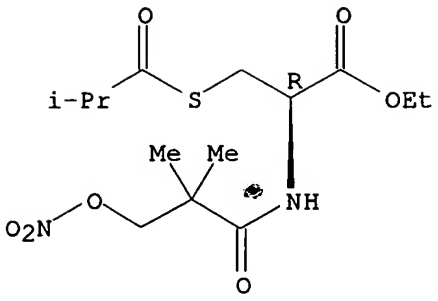
RN 130432-20-1 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, butanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



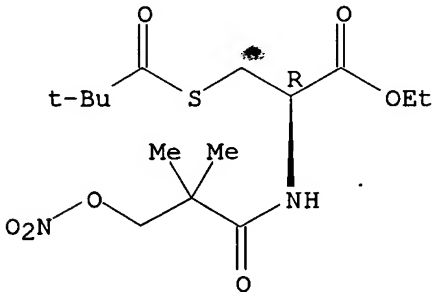
RN 130432-21-2 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, 2-methylpropanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



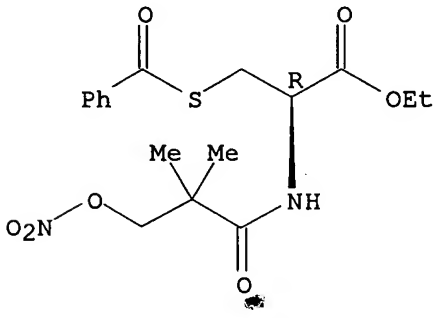
RN 130432-22-3 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, 2,2-dimethylpropanoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 130432-23-4 CAPLUS
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester, benzoate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



FILE 'CAOLD' ENTERED AT 12:21:30 ON 15 APR 2005
L6 0 S L4

FILE 'USPATFULL' ENTERED AT 12:21:36 ON 15 APR 2005
L7 7 S L4

L7 ANSWER 1 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2004:197447 USPATFULL
TITLE: Methods of use for novel sulfur containing organic nitrate compounds

INVENTOR(S):	Garvey, David S., Dover, MA, UNITED STATES Letts, L. Gordon, Dover, MA, UNITED STATES
PATENT ASSIGNEE(S):	NitroMed, Inc., Bedford, MA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004152753	A1	20040805
APPLICATION INFO.:	US 2004-760672	A1	20040121 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2002-US24923, filed on 7 Aug 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-311715P	20010810 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: EDWARD D GRIEFF, HALE & DORR LLP, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 1641
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention describes methods of use for an organic nitrate compound, or a pharmaceutically acceptable salt thereof, wherein the organic nitrate compound comprises at least one sulfur atom and/or at least one disulfide group. The invention also provides methods for treating, preventing and/or reducing inflammation, pain, and fever; for decreasing or reversing the gastrointestinal, renal and other toxicities resulting from the use of nonsteroidal antiinflammatory compounds; for treating and/or preventing gastrointestinal disorders; for treating inflammatory disease states and disorders; for treating and/or preventing ophthalmic diseases or disorders; for treating and/or improving the gastrointestinal properties of COX-2 inhibitors; for facilitating wound healing; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; for decreasing the recurrence of ulcers; for improving gastroprotective properties, anti-Helicobacter pylori properties or antacid properties of proton pump inhibitors; for treating Helicobacter pylori and viral infections; for improving gastroprotective properties of H.sub.2 receptor antagonists; for treating and/or preventing inflammations and microbial infections, multiple sclerosis, and viral infections; for treating or preventing restenosis, autoimmune diseases, pathological conditions resulting from abnormal cell proliferation, polycystic kidney disease, inflammatory diseases or to inhibit wound contraction; for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females; for treating or preventing benign prostatic hyperplasia, hypertension, congestive heart failure, variant (Printzmetal) angina, glaucoma, neurodegenerative disorders, vasospastic diseases, cognitive disorders, urge incontinence, and overactive bladder; for reversing the state of anesthesia; for treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP); for treating respiratory disorders and for treating neurological conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 2 OF 7 USPATFULL on STN

ACCESSION NUMBER: 2002:116286 USPATFULL
TITLE: Nitric oxide releasing chelating agents and their therapeutic use
INVENTOR(S): Towart, Robertson, Stoke Poges, UNITED KINGDOM
Karlsson, Jan Olof Gustav, Nesoddtangen, NORWAY
Wistrand, Lars Goran, Lund, SWEDEN
Malmgren, Hakan, Lund, SWEDEN
PATENT ASSIGNEE(S): Amersham Health AS, Oslo, NORWAY (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6391895	B1	20020521
APPLICATION INFO.:	US 2000-599862		20000623 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 1998-GB3804, filed on 18 Dec 1998		

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1997-27226	19971223
	GB 1998-5450	19980313
	US 1998-76793P	19980304 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Aulakh, Charanjit S.
LEGAL REPRESENTATIVE: Ronning, Jr., Royal N.
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 1100
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Chelating agents, in particular dipyridoxyl and aminopolycarboxylic acid based chelating agents, and their metal chelates, when linked directly or indirectly to at least one nitric oxide releasing moiety, or when use in combination with nitric oxide or a nitric oxide releasing moiety have been found to be effective in treating a variety of disorders. In particular, such compounds may be used in treating conditions associated with the presence of free radicals in the body, e.g. reperfusion injuries, and in reducing the cardiotoxicity of anti-tumor agents, e.g. anthracyclines and/or paclitaxel.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2000:150166 USPATFULL
TITLE: Tetracyclic cyclic GMP-specific phosphodiesterase inhibitors, process of preparation and use
INVENTOR(S): Daugan, Alain Claude-Marie, Marly le Roi Cedex, France
Gellibert, Francoise, Marly le Roi Cedex, France
PATENT ASSIGNEE(S): ICOS Corporation, Bothell, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6143746		20001107
APPLICATION INFO.:	US 1998-154051		19980916 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 1995-EP183,		

filed on 19 Jan 1995, now patented, Pat. No. WO 5859006 which is a continuation-in-part of Ser. No. WO 1996-EP3025, filed on 11 Jul 1996, now patented, Pat. No. WO 5981527 which is a continuation-in-part of Ser. No. WO 1996-EP3024, filed on 11 Jul 1996

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1994-1090	19940121
	GB 1995-14465	19950714
	GB 1995-14474	19950714

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Cintins, Marianne M.
ASSISTANT EXAMINER: Delacroix-Muirheid, C.
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 3174
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A compound of formula (I) and salts and solvates thereof, in which: R.sup.0 represents hydrogen, halogen, or C.sub.1-6 alkyl; R.sup.1 represents hydrogen, C.sub.1-6 alkyl, C.sub.2-6 alkenyl, C.sub.2-6 alkynyl, haloC.sub.1-6 alkyl, C.sub.3-8 cycloalkyl, C.sub.3-8 cycloalkylC.sub.1-3 alkyl, arylC.sub.1-3 alkyl, or heteroarylC.sub.1-3 alkyl; R.sup.2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or an optionally substituted bicyclic ring (a) attached to the rest of the molecule via one of the benzene ring carbon atoms, and wherein the fused ring (A) is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur, and nitrogen; and R.sup.3 represents hydrogen or C.sub.1-3 alkyl, or R.sup.1 and R.sup.3 together represent a 3- or 4-membered alkyl or alkenyl chain. A compound of formula (I) is a potent and selective inhibitor of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 7 USPATFULL on STN
ACCESSION NUMBER: 1999:132893 USPATFULL
TITLE: Pharmaceutical preparations and medicaments for the prevention and treatment of endothelial dysfunction
INVENTOR(S): Noack, Eike Albrecht, Neuss, Germany, Federal Republic of
Kojda, Georg, Koln, Germany, Federal Republic of
PATENT ASSIGNEE(S): ISIS PHARMA GmbH, Zwickau, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5973011		19991026	
APPLICATION INFO.:	US 1996-721465		19960927	(8)

	NUMBER	DATE

PRIORITY INFORMATION:	DE 1994-4410997	19940330
	WO 1995-DE421	19950328
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Criares, Theodore J.	
LEGAL REPRESENTATIVE:	Marshall, O'Toole, Gerstein, Murray & Borun	
NUMBER OF CLAIMS:	7	
EXEMPLARY CLAIM:	1	
LINE COUNT:	608	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention describes the use of nitric-oxide-liberating or transferring compounds, stimulators of endogenous NO formation, as well as stimulators of guanylate cyclase, for prevention, treatment and elimination of endothelial dysfunctions and the diseases accompanying these dysfunctions or caused by them, as well as the use of said compounds to produce pharmaceutical products for the cited areas of application.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 5 OF 7 USPATFULL on STN

ACCESSION NUMBER:	97:76111 USPATFULL			
TITLE:	Organic nitrates containing a disulfide group as cardiovascular agents			
INVENTOR(S):	Feelisch, Martin, Erkrath, Germany, Federal Republic of Bokens, Hilmar, Dusseldorf, Germany, Federal Republic of Lehmann, Jochen, Bonn, Germany, Federal Republic of Meese, Claus, Monheim, Germany, Federal Republic of Sandrock, Klaus, Langenfeld, Germany, Federal Republic of			
PATENT ASSIGNEE(S):	Schwarz Pharma AG, Germany, Federal Republic of (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5661129		19970826	
	WO 9500477		19950105	
APPLICATION INFO.:	US 1995-557106		19951205	(8)
	WO 1994-DE726		19940624	
			19951205	PCT 371 date
			19951205	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1993-4321306	19930626
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Tsang, Cecilia J.	
ASSISTANT EXAMINER:	Celsa, Bennett	
LEGAL REPRESENTATIVE:	Merchant, Gould, Smith, Edell, Welter & Schmidt, P.A.	
NUMBER OF CLAIMS:	13	
EXEMPLARY CLAIM:	1	
LINE COUNT:	952	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to novel nitrates containing a disulphide

group, and to processes for their preparation. The compounds can be used for the therapy of disorders of the cardiovascular system.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 6 OF 7 USPATFULL on STN
ACCESSION NUMBER: 95:58163 USPATFULL
TITLE: Organic nitrates and method for their preparation
INVENTOR(S): Sandrock, Klaus, Langenfeld, Germany, Federal Republic of
Hutter, Joachim, Leverkusen, Germany, Federal Republic of
Noack, Eike, Neuss, Germany, Federal Republic of
PATENT ASSIGNEE(S): Schwarz Pharma AG, Monheim, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5428061		19950627	
APPLICATION INFO.:	US 1993-116946		19930907	(8)

DISCLAIMER DATE: 20110208
RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-818502, filed on 8 Jan 1992, now abandoned which is a continuation-in-part of Ser. No. US 1989-406165, filed on 12 Sep 1989, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1988-38313111	19880915

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: O'Sullivan, Peter
ASSISTANT EXAMINER: Burn, Brian M.
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1083
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB New organic nitrate compounds, formed by condensing a nitrato alkanoic acid with a sulfur-containing amino acid or peptide, which prevent nitrate tolerance or overcome existing tolerance and which are useful for the treatment of cardiac diseases including circulatory diseases, high blood pressure, cardiac insufficiency and for dilating the peripheral vessels.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 7 OF 7 USPATFULL on STN
ACCESSION NUMBER: 94:11440 USPATFULL
TITLE: Nitrato alkanoic acid derivatives, methods for their production, pharmaceutical compositions containing the derivatives and medicinal uses thereof
INVENTOR(S): Sandrock, Klaus, Langenfeld, Germany, Federal Republic of
Noack, Eike, Neuss, Germany, Federal Republic of
Fritschi, Edgar, Schwalmtal-Luttelforst, Germany, Federal Republic of

Kanzler, Ralf, Leverkusen, Germany, Federal Republic of
Feelisch, Martin, Dusseldorf, Germany, Federal Republic of
PATENT ASSIGNEE(S): Schwarz Pharma AG, Monheim, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5284872		19940208
APPLICATION INFO.:	US 1991-681876		19910405 (7)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1989-406165, filed on 12 Sep 1989, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1990-4011505	19900410

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Waddell, Frederick E.
ASSISTANT EXAMINER: Hook, Gregory
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 552

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB New organic nitrate compounds, formed by condensing a nitrato alkanoic acid with a sulfur-containing amino acid or peptide followed by the reaction of the resulting product with an amino acid, N-acylamino acid, peptide or an N-acyl peptide to produce a thio ester thereof, which prevent nitrate tolerance or overcome existing tolerance and which are useful for the treatment of cardiac diseases including circulatory diseases, coronary dilation, high blood pressure, cardiac insufficiency and for dilating the peripheral vessels.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

(FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 12:22:01 ON 15 APR 2005)

L8 43 SEA ABB=ON PLU=ON L4

L9 0 SEA ABB=ON PLU=ON L8 AND (PEPTIC OR UCLER? OR GASTROINTESTIN? OR GASTR? INTESTIN? OR (INTESTIN? OR GASTR## OR STOMACH)(S)(DISORDER OR DISEAS?))

L10 25 SEA ABB=ON PLU=ON L8 AND (TREAT? OR THERAP? OR PREVENT?)

L11 20 DUP REM L10 (5 DUPLICATES REMOVED)

L11 ANSWER 1 OF 20 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2001028906 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11046123
TITLE: Inhibition of endothelial cell activation by nitric oxide donors.
AUTHOR: Zampolli A; Basta G; Lazzerini G; Feelisch M; De Caterina R
CORPORATE SOURCE: Consiglio Nazionale delle Ricerche Institute of Clinical Physiology Laboratory for Thrombosis and Vascular Research, Pisa, Italy.
SOURCE: Journal of pharmacology and experimental therapeutics, (2000 Nov) 295 (2) 818-23.

Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001121

AB Because nitric oxide (NO) inhibits the expression of endothelial leukocyte adhesion molecules, NO-generating compounds have major **therapeutic** potential for use outside their classical indications. We report on the in vitro potential antiatherogenicity of two novel cysteine-containing NO donors, SP/W 3672, a fast spontaneous NO releaser, and its prodrug SP/W 5186, which liberates NO after bioactivation. The ability of these two compounds to inhibit monocyte adhesion and surface expression of endothelial adhesion molecules was evaluated and compared with that of other NO donors. SP/W 5186 and SP/W 3672 inhibited the adhesion of U937 monocytes to cultured human endothelial cells more potently than S-nitrosoglutathione (GSNO) or spermine NONOate, whereas nitroglycerin and isosorbide dinitrate were ineffective at comparable concentrations. A similar rank order of potency was found for the inhibition of expression of the adhesion molecules vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin as well as for major histocompatibility complex class II antigen expression. Estimated IC(50) values for vascular cell adhesion molecule-1 were >400 microM for SP/W 4744 (control for SP/W 3672 lacking the cysteine moiety), 200 microM for GSNO and spermine NONOate, 80 microM for SP/W 3672, and 50 microM for SP/W 5186. Moreover, SP/W 5186 inhibited VCAM-1 mRNA levels more potently than GSNO. This effect was likely to be transcriptional because mRNA degradation was not affected. In conclusion, SP/W 3672 and SP/W 5186 are novel potent inhibitors of endothelial activation, and this effect appears to relate to their ability to liberate NO for prolonged periods of time, either spontaneously or after conversion to active hydrolytic products.

L11 ANSWER 2 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:26739 BIOSIS
DOCUMENT NUMBER: PREV199900026739
TITLE: SP/W-5186, A cysteine-containing nitric oxide donor, attenuates postischemic myocardial injury.
AUTHOR(S): Liu, Gao-Lin; Christopher, Theodore A.; Lopez, Bernard L.; Gao, Feng; Guo, Yaping; Gao, Erhe; Knuettel, Karlheinz; Feelisch, Martin; Ma, Xin L. [Reprint author]
CORPORATE SOURCE: Div. Emergency Med., Jefferson Med. Coll., 1020 Sansom St., Philadelphia, PA 19107-5004, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (Nov., 1998) Vol. 287, No. 2, pp. 527-537. print.
CODEN: JPETAB. ISSN: 0022-3565.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jan 1999
Last Updated on STN: 20 Jan 1999

AB The effects of SP/W-5186, a cysteine-containing nitric oxide (-NO) donor, on myocardial reperfusion injury were studied in a rabbit

ischemia (45 min) and reperfusion (180 min) model. Five min before reperfusion, either low-dose (0.3 mumol/kg) or high-dose (1 mumol/kg) SP/W-5186 was given intravenously as a bolus. Administration of 0.3 mumol/kg SP/W-5186 did not change mean arterial blood pressure, heart rate or pressure rate index. However, administration of low-dose SP/W-5186 exerted marked cardioprotective effects as evidenced by improved cardiac functional recovery ($P < .05$ vs. vehicle), decreased plasma creatine kinase concentration ($P < .01$) and reduced infarct size ($P < .01$). Moreover, administration of SP/W-5186 significantly decreased platelet aggregation ($P < .01$ vs. vehicle), attenuated polymorphonuclear leukocyte (PMN) accumulation in myocardial tissue, inhibited PMN adhesion to endothelial cells and preserved endothelial function. Administration of high-dose SP/W-5186 resulted in a transient but significant decrease in mean arterial blood pressure and exerted more cardiac protection compared with low-dose **treatment**. However, the effects on platelet aggregation, PMN accumulation and PMN adhesion did not differ significantly between the two SP/W-5186 groups. Furthermore, administration of SP/W-6373, an analogue of SP/W-5186 that lacks the NO moiety, failed to exert any protective effects. These results demonstrate that NO released from SP/W-5186 significantly protected myocardial tissue from reperfusion injury. The primary mechanisms of the observed cardioprotection by SP/W-5186 involve inhibition of platelet aggregation, attenuation of PMN-endothelium interaction and preservation of endothelial function.

L11 ANSWER 3 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:108617 BIOSIS
DOCUMENT NUMBER: PREV199900108617
TITLE: SP/W-5186: A novel sulfhydryl-containing NO donor.
AUTHOR(S): Bonn, R. [Reprint author]; Scharfenecker, U.; Friehe, H.; Gerloff, J.
CORPORATE SOURCE: Clinical Pharmacology, Schwarz Pharma AG, Alfred-Nobel-Strasse 10, D-40789 Monheim Rhein, Germany
SOURCE: Cardiovascular Drug Reviews, (Fall, 1998) Vol. 16, No. 3, pp. 195-211. print.
ISSN: 0897-5957.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Mar 1999
Last Updated on STN: 4 Mar 1999

L11 ANSWER 4 OF 20 MEDLINE on STN

ACCESSION NUMBER: 97406580 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9260003
TITLE: The effect of chronic **treatment** with NO donors during intimal thickening and fatty streak formation.
AUTHOR: De Meyer G R; Bult H; Kockx M M; Herman A G
CORPORATE SOURCE: Division of Pharmacology, University of Antwerp, Belgium.
SOURCE: BioFactors (Oxford, England), (1997) 6 (2) 209-15.
Journal code: 8807441. ISSN: 0951-6433.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710

Searcher : Shears 571-272-2528

ENTRY DATE: Entered STN: 19971024
Last Updated on STN: 19971024
Entered Medline: 19971014

AB Intimal thickening in arteries is considered as a site of predilection for atherosclerosis. We investigated whether oral application of the nitric oxide (NO) donors SPM-5185 (N-nitratopivaloyl-S-(N'-acetylalanyl)-cysteine ethylester, 10 mg/kg body weight/b.i.d.) and molsidomine (pro-drug of 3-morpholino-sydnonimine (SIN-1), 10 mg/kg body weight/day) can retard intimal thickening and changes in vascular reactivity induced by a silicone collar positioned around the carotid artery of rabbits. Intimal thickening was significantly inhibited by SPM-5185 (cross-sectional area 18 +/- 6 vs. 44 +/- 10 x 10(-3) mm2; P < 0.05), but not by molsidomine (28 +/- 6 vs. 35 +/- 9 x 10(-3) mm2), which is a donor of both NO and superoxide anions. In organ chamber studies collaring was associated with a decreased sensitivity to acetylcholine (ACh). SPM-5185 evoked a tendency towards normalization of the pD2 of ACh in collared arteries. We also investigated whether chronic nitric oxide (NO) **treatment** affected vascular reactivity and fatty streak development in the rabbit aorta. During 16 weeks rabbits received 150 g/day of a standard diet, or diets with 0.3% cholesterol, with 0.02% molsidomine (10 mg/kg body weight/day) or with the combination. The NO donor enhanced the area of fatty streaks, without affecting hypercholesterolemia. Moreover, it desensitized the smooth muscle cells of the rabbit aorta to vasodilators acting via the cytoplasmic guanylate cyclase and suppressed the capacity of the endothelial cells to release NO in response to muscarinic receptor stimulation. This suggested that chronic exposure to large quantities of NO caused a negative feedback, with selective decreases of both the endothelial capacity to generate NO and the responsiveness to vasodilators operating via cyclic GMP. In conclusion, we demonstrated that exogenous NO can decrease intimal hyperplasia in vivo. However, prolonged in vivo **treatment** with a donor of NO enhanced atherosclerosis in hypercholesterolemic rabbits.

L11 ANSWER 5 OF 20 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 96160975 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8590999
TITLE: Specificity of different organic nitrates to elicit NO formation in rabbit vascular tissues and organs in vivo.
AUTHOR: Mulsch A; Bara A; Mordvintcev P; Vanin A; Busse R
CORPORATE SOURCE: Zentrum der Physiologie, Universitat Frankfurt, Germany.
SOURCE: British journal of pharmacology, (1995 Nov) 116 (6) 2743-9.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19960418
Last Updated on STN: 20000303
Entered Medline: 19960404

AB 1. In the present study we assessed the formation of nitric oxide (NO) from classical and thiol-containing organic nitrates in vascular tissues and organs of anaesthetized rabbits, and established a relationship between the relaxant response elicited by nitroglycerin

(NTG) and NO formation in the rabbit isolated aorta. Furthermore, the effect of isolated cytochrome P450 on NO formation from organic nitrates was investigated. 2. Rabbits received diethyldithiocarbamate (DETC; 200 mg kg-1 initial bolus i.p. and 200 mg kg-1 during 20 min, i.v.) and either saline, or one of the following organic nitrates: nitroglycerin (NTG, 0.5 mg kg-1), isosorbide dinitrate (ISDN), N-(3-nitratopivaloyl)-L-cysteine ethylester (SPM 3672), S-carboxyethyl-N-(3-nitratopivaloyl)-L-cysteine ethylester (SPM 5185), at 10 mg kg-1 each. After 20 min the animals were killed, blood vessels and organs were removed, and subsequently analyzed for spin-trapped NO by cryogenic electron spin resonance (e.s.r.) spectroscopy. 3. In the saline-**treated** control group, NO remained below the detection limit in all vessels and organs. In contrast, all of the nitrates tested elicited measurable NO formation, which was higher in organs (liver, kidney, heart, lung, spleen) (up to 4.8 nmol g-1 20 min-1) than in blood vessels (vena cava, mesenteric bed, femoral artery, aorta) (up to 0.7 nmol g-1 20 min-1). Classical organic nitrates (NTG, ISDN) formed NO preferentially in the mesenteric bed and the vena cava, while the SPM compounds elicited comparable NO formation in veins and arteries. 4. Using a similar spin trapping technique, NO formation was assessed in vitro in phenylephrine-precontracted rabbit aortic rings. The maximal relaxation elicited by a first exposure (10 min) to NTG (0.3 to 10 microM) was positively correlated (r = 0.8) with the net increase (NTG minus basal) of NO spin-trapped during a second exposure to the same concentration of NTG in the presence of DETC. 5. Cytochrome P450 purified from rabbit liver enhanced NO formation in a NADPH-dependent fashion from NTG, but not from the other nitrates, as assessed by activation of purified soluble guanylyl cyclase. 6. We conclude that the vessel selective action of different organic nitrates in vivo reflects differences in vascular NO formation. Thus, efficient preload reduction by classical organic nitrates can be accounted for by higher NO formation in venous capacitance as compared to arterial conductance and resistance vessels. In contrast, NO is released from cysteine-containing nitrates (SPMs) to a similar extent in arteries and veins, presumably independently of an organic nitrate-specific biotransformation. Limited tissue bioavailability of NTG and ISDN might account for low NO formation in the aorta, while true differences in biotransformation seem to account for differences in NO formation in the other vascular tissues.

L11 ANSWER 6 OF 20 MEDLINE on STN
ACCESSION NUMBER: 95295329 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7776679
TITLE: Blood cardioplegia enhanced with nitric oxide donor SPM-5185 counteracts postischemic endothelial and ventricular dysfunction.
AUTHOR: Nakanishi K; Zhao Z Q; Vinten-Johansen J; Hudspeth D A; McGee D S; Hammon J W Jr
CORPORATE SOURCE: Department of Cardiothoracic Surgery, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, N.C., USA.
CONTRACT NUMBER: HL46179 (NHLBI)
SOURCE: Journal of thoracic and cardiovascular surgery, (1995 Jun) 109 (6) 1146-54.
Journal code: 0376343. ISSN: 0022-5223.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

Searcher : Shears 571-272-2528

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950720
Last Updated on STN: 19950720
Entered Medline: 19950707

AB This study tested the hypothesis that enhancement of blood cardioplegia with the nitric oxide donor agent SPM-5185 inhibits postischemic left ventricular and coronary endothelial dysfunction. Eighteen anesthetized dogs supported by total vented bypass were subjected to 30 minutes of normothermic ischemia followed by 4 degrees C multidose blood cardioplegia. Hearts received either standard blood cardioplegia (vehicle group; n = 6), blood cardioplegia with 1 mumol/L SPM-5185 (low-dose group; n = 6), or 10 mumol/L SPM-5185 (high-dose group; n = 6). After 60 minutes of cardioplegic arrest, the heart was reperfused for a total of 60 minutes, first in the beating empty state for 30 minutes and then after discontinuation of bypass for 30 minutes. Baseline and postischemic left ventricular function was assessed by the slope of the end-systolic pressure-volume (impedance catheter) relation. Postischemic end-systolic pressure-volume relation was depressed by 53.7% of preischemic values in the vehicle group (from 8.2 +/- 1.0 to 3.8 +/- 0.3 mm Hg/ml) and by 33.7% (from 9.2 +/- 1.1 to 6.1 +/- 0.5 mm Hg/ml) in the low-dose group. In contrast, there was complete postischemic functional recovery in the high-dose group (from 7.6 +/- 1.1 to 7.2 +/- 1.2 mm Hg/ml). In coronary arteries isolated from these hearts, endothelium-dependent maximal relaxation to acetylcholine was impaired by 27% in the vehicle group and by 18% in the low-dose group, whereas the high-dose group showed complete endothelium-dependent relaxation. Myeloperoxidase activity, an index of neutrophil accumulation in postischemic myocardium, was elevated in the vehicle and low-dose groups (3.36 +/- 0.58 and 2.56 +/- 0.68 U/100 mg tissue) but was significantly reduced in the high-dose group to 1.27 +/- 0.45 U/100 mg tissue. We conclude that inclusion of 10 mumol/L nitric oxide donor SPM-5185 in blood cardioplegia improves postischemic ventricular performance and endothelial function in ischemically injured hearts, possibly via inhibition of neutrophil-mediated damage.

L11 ANSWER 7 OF 20 MEDLINE on STN
ACCESSION NUMBER: 96015201 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7579837
TITLE: Augmentation of microvascular nitric oxide improves myocardial performance following global ischemia.
AUTHOR: Hammon J W Jr; Vinten-Johansen J
CORPORATE SOURCE: Department of Cardiothoracic Surgery, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27157-1096, USA.
CONTRACT NUMBER: HL46179 (NHLBI)
SOURCE: Journal of cardiac surgery, (1995 Jul) 10 (4 Suppl) 423-7.
Journal code: 8908809. ISSN: 0886-0440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951127

AB Hearts exposed to global myocardial ischemia associated with cardiac

surgery often suffer postischemic endothelial and contractile dysfunction related to antecedent regional or global ischemia. Our studies tested the hypothesis that supplementing blood cardioplegia and reperfusion with the nitric oxide (NO) precursor L-arginine or the NO donor SPM-5185 would preserve endothelial function, reduce infarct size, and reverse postcardioplegia regional contractile dysfunction or global dysfunction. In the first study involving 23 anesthetized dogs undergoing regional ischemia, supplementation of blood cardioplegia with L-arginine: (1) reduced infarct size; (2) improved postischemic regional segmental work and diastolic stiffness; (3) attenuated neutrophil accumulation in the area at risk; and (4) improved postischemic depressed coronary artery endothelial function. The NO synthase inhibitor N-nitro-L-arginine (L-NA) reversed these protective effects. In another experiment involving 18 anesthetized dogs undergoing normothermic global ischemia, hearts **treated** with blood cardioplegia supplemented with the NO donor SPM-5185 demonstrated better postischemic coronary artery endothelial function, lowered myeloperoxidase activity in the ischemic-reperfused myocardium, and significantly improved global ventricular function in the group receiving high-dose SPM-5185. We conclude that the inclusion of L-arginine or high-dose NO donor SPM-5185 in blood cardioplegia improves postischemic ventricular performance and endothelial function in ischemically injured hearts, possibly by inhibition of neutrophil-mediated damage via the L-arginine-NO pathway.

L11 ANSWER 8 OF 20 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 96058636 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8583781
TITLE: Development of nitrate tolerance in human arteries and veins: comparison of nitroglycerin and SPM 5185.
AUTHOR: Arnet U; Yang Z; Siebenmann R; von Segesser L K; Turina M; Stulz P; Luscher T F
CORPORATE SOURCE: Department of Research, University Hospitals, Basel, Switzerland.
SOURCE: Journal of cardiovascular pharmacology, (1995 Sep) 26 (3) 401-6.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960327
Last Updated on STN: 19960327
Entered Medline: 19960321

AB Nitrate tolerance is a clinical problem in patients with coronary artery disease and heart failure. Human internal mammary arteries and saphenous veins obtained intraoperatively were suspended in organ chambers, and isometric tension was measured. In the artery, nitroglycerin elicited a potent relaxation, which was significantly diminished after prolonged incubation with nitroglycerin (10(-6) M, 1 h). In contrast, no tolerance occurred in saphenous vein under the same conditions. However, incubation with 10(-5) M nitroglycerin also developed tolerance. Compared to nitroglycerin, the new cysteine-containing mononitrate SPM 5185 exhibited a lower sensitivity but comparable maximal relaxation in arteries and veins. In nitroglycerin-tolerant arteries and veins, SPM 5185 caused relaxations similar to those under control conditions. Our results show that in

isolated blood vessels, vascular nitrate tolerance occurs more readily in the mammary artery than in the saphenous vein. SPM 5185 seems to be less prone to the development of tolerance, which may be advantageous during chronic nitrate **therapy**.

L11 ANSWER 9 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96116649 EMBASE
DOCUMENT NUMBER: 1996116649
TITLE: Sulfhydryl-containing nitrate esters: A new class of nitric oxide donors.
AUTHOR: Kojda G.; Feelisch M.; Noack E.
CORPORATE SOURCE: Institut fur Pharmakologie, Medizinische Einrichtungen, Heinrich-Heine Universitat, Moorenstrasse 5,Dusseldorf 40225, Germany
SOURCE: Cardiovascular Drug Reviews, (1995) Vol. 13, No. 3, pp. 275-288.
ISSN: 0897-5957 CODEN: CDREEA
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 960430
Last Updated on STN: 960430

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L11 ANSWER 10 OF 20 MEDLINE on STN

ACCESSION NUMBER: 96103968 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8537152
TITLE: The role of nitric oxide and NO-donor agents in myocardial protection from surgical ischemic-reperfusion injury.
AUTHOR: Vinten-Johansen J; Sato H; Zhao Z Q
CORPORATE SOURCE: Department of Cardiothoracic Surgery, Bowman Gray School of Medicine, Winston-Salem, NC 27157-1096, USA.
CONTRACT NUMBER: HL46179 (NHLBI)
SOURCE: International journal of cardiology, (1995 Jul) 50 (3) 273-81. Ref: 47
Journal code: 8200291. ISSN: 0167-5273.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960221
Last Updated on STN: 19980206
Entered Medline: 19960206

AB The coronary vascular endothelium is injured by ischemia-reperfusion, which may facilitate the pathophysiological role played by neutrophils. Hearts undergoing coronary artery bypass surgery or other surgical procedures requiring cardiopulmonary bypass and elective cardioplegia undergo repetitive episodes of ischemia and

reperfusion, which leads to endothelial injury as well as contractile dysfunction and morphological injury, despite the use of cardioprotective cardioplegic solutions and other strategies of myocardial protection. In cardiac surgery, as in coronary occlusion, endothelial injury seems to occur upon reperfusion with unmodified blood. Blood cardioplegia does not **prevent** this surgical 'reperfusion injury', but does **prevent** extension of endothelial injury during the period of hypothermic cardioplegic arrest ('protected ischemia'). It is not known whether global cardioplegic ischemia in preoperatively injured hearts impairs the basal release of nitric oxide (NO) and hence obtunds this endogenous protective mechanism. However, enhancement of blood cardioplegia with the NO precursor, L-arginine, reduces postsurgical myocardial injury, suggesting that endogenous or basal release of NO participates in the modulation of ischemic-reperfusion injury. In addition, an NO-donor agent also protects the myocardium from surgical ischemic-reperfusion injury. Both cardioprotective strategies involve inhibition of neutrophil accumulation, consistent with the known inhibitory effects of NO on neutrophil adherence and neutrophil-mediated damage to the coronary endothelium. Therefore, NO-related **therapy** offers a new strategy to protect the myocardium, including the coronary endothelium, from surgically imposed ischemic-reperfusion injury.

L11 ANSWER 11 OF 20 MEDLINE on STN
ACCESSION NUMBER: 96078509 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7475052
TITLE: Effect of nitric oxide donors on neointima formation and vascular reactivity in the collared carotid artery of rabbits.
AUTHOR: De Meyer G R; Bult H; Ustunes L; Kockx M M; Feelisch M; Herman A G
CORPORATE SOURCE: Division of Pharmacology, University of Antwerp, Belgium.
SOURCE: Journal of cardiovascular pharmacology, (1995 Aug) 26 (2) 272-9.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951207

AB Intimal thickening in arteries is considered a site of predilection for atherosclerosis. We investigated whether oral application of the nitric oxide (NO) donors SPM-5185 [N-nitratopivaloyl-S-(N'-acetylalanyl)-cysteine ethylester, 10 mg/kg body weight twice daily (b.i.d.)] and molsidomine (10 mg/kg body weight/day) can retard neointima formation and changes in vascular reactivity induced by a nonocclusive, soft silicone collar positioned around the left carotid artery of rabbits. The contralateral carotid artery was sham operated and served as a control. Drug and placebo (diet without drug) **treatments** were initiated 7 days before placement of the collar. At the end of the experiments, two segments were cut from each collared and sham-**treated** artery, one for measurement of the cross-sectional area of intima and media and the other for isometric tension recording. Sham **treatment** did not result in intimal thickening in either group. In contrast, the intima/media

(I/M) ratio was considerably increased after 14 days of collar **treatment** as a result of neointima formation. Intimal thickening was significantly inhibited by SPM-5185 (I/M ratio 0.05 +/- 0.01 vs. 0.11 +/- 0.02, $p < 0.05$), but not by molsidomine (0.06 +/- 0.02 vs. 0.08 +/- 0.02, $p = 0.49$), which is a donor of both NO and superoxide anions. Neither collar nor NO donor **treatment** altered the area of the media. SPM-5185 did not alter the percentage of replicating smooth muscle cells (SMC) in the media after collar **treatment**, as demonstrated by their immunoreactivity for proliferating cell nuclear antigen (PCNA).(ABSTRACT TRUNCATED AT 250 WORDS)

L11 ANSWER 12 OF 20 MEDLINE on STN
ACCESSION NUMBER: 95219457 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7704591
TITLE: Myocardial protective actions of nitric oxide donors after myocardial ischemia and reperfusion.
AUTHOR: Lefer D J
CORPORATE SOURCE: Department of Medicine, Tulane University School of Medicine, New Orleans, LA 70112, USA.
CONTRACT NUMBER: F-32-HL-08616 (NHLBI)
SOURCE: New horizons (Baltimore, Md.), (1995 Feb) 3 (1) 105-12. Ref: 53
Journal code: 9416195. ISSN: 1063-7389.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19950518
Entered Medline: 19950509

AB Coronary artery ischemia initiated by occlusion or thrombus formation produces myocardial ischemia that can ultimately result in myocardial cell injury and necrosis of the myocardium. Current clinical strategies for the **treatment** of acute myocardial ischemia include coronary angioplasty, directional coronary atherectomy, and the administration of thrombolytic agents to restore blood flow to the ischemic myocardium. While coronary reperfusion can salvage ischemic tissue, it may in itself also contribute to coronary vascular and myocardial cell injury (1-4). Myocardial reperfusion after coronary artery ischemia accelerates the necrosis of reversibly injured cardiac myocytes by enhancing cell swelling, the disruption of cell ultrastructure, formation of contraction bands, and the influx of calcium and other ions (2, 3). Recent experimental evidence strongly suggests that coronary artery endothelial dysfunction may be an early trigger for neutrophil-mediated myocardial reperfusion injury (4-7). Nitric oxide (NO.) release by the coronary vasculature is impaired within 5 mins after reperfusion of ischemic myocardium and results in a profound loss of vascular homeostasis (7). Polymorphonuclear neutrophils (PMN) begin to accumulate within the ischemic-reperfusion myocardium as a result of diminished coronary NO. release; activated PMNs then mediate myocardial cell injury and necrosis (6, 7). Novel **therapeutic** strategies aimed at the preservation or replenishment of coronary NO. concentrations may prove beneficial in the **treatment** of myocardial reperfusion injury in the future.(ABSTRACT TRUNCATED AT 250 WORDS)

Searcher : Shears 571-272-2528

L11 ANSWER 13 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 95349507 EMBASE
DOCUMENT NUMBER: 1995349507
TITLE: [Nitrogen oxide in the **treatment** of nervous diseases and vascular diseases].
NO: **THERAPEUTIKUM** BEI NERVEN- UND GEFASSKRANKHEITEN.
AUTHOR: Rucker D.
CORPORATE SOURCE: Germany
SOURCE: Pharmazeutische Zeitung, (1995) Vol. 140, No. 47, pp. 62-63.
ISSN: 0031-7136 CODEN: PZSED5
COUNTRY: Germany
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: German
ENTRY DATE: Entered STN: 951228
Last Updated on STN: 951228
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L11 ANSWER 14 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 94322348 EMBASE
DOCUMENT NUMBER: 1994322348
TITLE: The possibilities for novel **therapies**: The L-arginine to nitric oxide pathway.
AUTHOR: Wilson C.A.J.
CORPORATE SOURCE: Department of Obstetrics/Gynaecology, St. George's Hosp. Medical School, Cranmer Terrace,London SW17 0RE, United Kingdom
SOURCE: Pharmaceutical Medicine, (1994) Vol. 8, No. 1-2, pp. 49-63.
ISSN: 0265-0673 CODEN: PHMDEH
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 002 Physiology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 941116
Last Updated on STN: 941116
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L11 ANSWER 15 OF 20 MEDLINE on STN
ACCESSION NUMBER: 94037385 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8222138

TITLE: Cytoprotective effects of nitric oxide.
COMMENT: Comment on: Circulation. 1993 Nov;88(5 Pt 1):2337-50.
PubMed ID: 8222127
AUTHOR: Cooke J P; Tsao P S
SOURCE: Circulation, (1993 Nov) 88 (5 Pt 1) 2451-4.
Journal code: 0147763. ISSN: 0009-7322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 20021210
Entered Medline: 19931203

L11 ANSWER 16 OF 20 MEDLINE on STN
ACCESSION NUMBER: 94037374 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8222127
TITLE: Antineutrophil and myocardial protecting actions of a novel nitric oxide donor after acute myocardial ischemia and reperfusion of dogs.
COMMENT: Comment in: Circulation. 1993 Nov;88(5 Pt 1):2451-4.
PubMed ID: 8222138
AUTHOR: Lefer D J; Nakanishi K; Johnston W E; Vinten-Johansen J
CORPORATE SOURCE: Department of Physiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157.
CONTRACT NUMBER: HL-36377 (NHLBI)
R29-40395
SOURCE: Circulation, (1993 Nov) 88 (5 Pt 1) 2337-50.
Journal code: 0147763. ISSN: 0009-7322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 20021210
Entered Medline: 19931203

AB BACKGROUND. It has recently been demonstrated that myocardial ischemia and reperfusion results in a marked decrease in the release of nitric oxide (NO) by the coronary endothelium. NO may possess cardioprotective properties, possibly related to inhibition of neutrophil-related activities. We tested the hypothesis that a cysteine-containing nitric oxide donor compound, SPM-5185, would reduce infarct size and inhibit neutrophil-related activities (adherence to coronary vascular endothelium, accumulation). METHODS AND RESULTS. The effects of intracoronary infusion of SPM-5185 were investigated in a 5.5-hour model of myocardial ischemia (1 hour) and reperfusion (4.5 hours) (MI-R) in anesthetized, open-chest dogs. SPM-5185 (500 nmol/L) or saline vehicle was infused for 4.5 hours into the left anterior descending coronary artery (LAD) at the time of reperfusion after 1 hour of LAD occlusion. MI-R in dogs receiving saline vehicle resulted in severe myocardial injury characterized by dyskinesis, a profound elevation of plasma creatine kinase, marked myocardial necrosis, and high cardiac myeloperoxidase (MPO) activity in the ischemic and necrotic zones. In contrast, **treatment** with SPM-5185 resulted in a modest restoration of regional function, a

reduction of myocardial necrosis expressed as a percentage of the area at risk (12.5 +/- 3.2% versus 41.7 +/- 5.4%, P < .001), and significant reductions of MPO activity in the ischemic zone (0.8 +/- 0.1 versus 2.5 +/- 0.7 U/100 mg tissue, P < .05) and the necrotic zone (1.6 +/- 0.2 versus 3.3 +/- 0.6 U/100 mg tissue, P < .05). In additional studies, SPM-5185 (500 nmol/L) significantly (P < .001) attenuated the adherence of LTB4-stimulated canine neutrophils to autologous segments of coronary artery and attenuated the neutrophil-induced contraction of isolated coronary arterial rings. CONCLUSIONS. SPM-5185 reduces myocardial necrosis and neutrophil accumulation in an acute model of canine myocardial ischemia and reperfusion. This reduction in myocardial cell injury may be partially related to the inhibitory actions of this novel NO donor on neutrophil adherence to the coronary endothelium.

L11 ANSWER 17 OF 20 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 94155966 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8112399
TITLE: Influence of endothelium and nitrovasodilators on free thiols and disulfides in porcine coronary smooth muscle.
AUTHOR: Kojda G; Meyer W; Noack E
CORPORATE SOURCE: Institut fur Pharmakologie, Heinrich-Heine Universitat, Dusseldorf, Germany.
SOURCE: European journal of pharmacology, (1993 Dec 21) 250 (3) 385-94.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940406
Last Updated on STN: 20000303
Entered Medline: 19940331

AB It is hypothesised that the well known development of tolerance to the vasodilating action of organic nitrates is contributed by intracellular depletion of free thiols occurring during repeated **treatment** with these drugs. Therefore, ring segments of porcine coronary arteries with and without endothelium were **treated** for 30 min with either vehicle or 100 microM of isosorbide-5-mononitrate, glyceryl trinitrate, S-nitroso-N-acetyl-D,L-penicillamine or N-(3-nitratopivaloyl)-1-cysteine-ethylester (SPM-3672), and the content of histochemically stained free thiols (-SH) and disulfides (S-S-) was measured densitometrically in single smooth muscle cells. In the presence of endothelium the content of -SH in smooth muscle cells of controls (n = 8) gave an extinction of 0.127 +/- 0.013 in the intima and 0.120 +/- 0.010 in the media. The corresponding values for S-S- were 0.684 +/- 0.084 and 0.535 +/- 0.120 (n = 8). Removal of endothelium reduced S-S- to 82.1 +/- 70% and increased -SH to 126.7 +/- 6.7%. **Treatment** with all nitrates reduced -SH in intact artery segments to a similar degree, ranging between 54.0 +/- 4.4 and 68.7 +/- 4.7% (n = 8-10). In contrast, S-S- content was less affected and reached values between 70.6 +/- 2.8 and 91.6 +/- 6.0% (n = 8-9). As evaluated by tension studies, tolerance developed for glycerol trinitrate and isosorbide-5-mononitrate but not for S-nitroso-N-acetyl-D,L-penicillamine. Induction of tolerance with glycerol trinitrate (0.1 mM) produced a significantly more pronounced attenuation in activity

of isosorbide-5-mononitrate than tolerance induction with isosorbide-5-mononitrate (1 mM). In contrast, the potency of SPM 3672 was not reduced in glycerol trinitrate-tolerant arteries. We conclude that, in porcine coronary arteries, an intact endothelium modifies intracellular thiols and disulfides. In addition, nitrate tolerance is associated with, but probably not caused by, thiol depletion.

L11 ANSWER 18 OF 20 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 93375690 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7690081
TITLE: Nitric oxide liberating, soluble guanylate cyclase stimulating and vasorelaxing properties of the new nitrate-compound SPM 3672.
AUTHOR: Kojda G; Noack E
CORPORATE SOURCE: Institut fur Pharmakologie, Heinrich-Heine Universitat, Dusseldorf, F.R.G.
SOURCE: Journal of cardiovascular pharmacology, (1993 Jul) 22 (1) 103-11.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931022
Last Updated on STN: 20000303
Entered Medline: 19931007

AB Development of tolerance as a consequence of organic nitrate **therapy** such as that which occurs with glyceryl trinitrate (GTN) appears to be associated with a depletion of free thiols in vascular smooth muscle. In this study, we investigated N-[3-nitratopivaloyl]-L-cysteineethylester (SPM 3672), a new compound containing a nitrate and a thiol moiety, in direct comparison with GTN. Liberation of nitric oxide (NO) from GTN and SPM 3672 measured in vitro was rather low and was markedly potentiated by addition of cysteine only in the case of GTN. Pronounced activation of a partially purified human soluble guanylate cyclase (sGC) by GTN was observed only after addition of cysteine, whereas a comparative activation by SPM 3672 occurred with and without addition of this thiol. In contrast, SPM 4946 (N(-)[3-hydroxypivaloyl]-L-cysteineethylester), a derivative of SPM 3672 lacking the nitrate-ester moiety, did not activate sGC. Activation of sGC by GTN and SPM 3672 was nearly abolished by oxyhemoglobin. Incubation of isolated porcine coronary artery rings with GTN or SPM 3672 resulted in a similar increase in vascular cyclic GMP levels. In rat aorta, GTN was a more potent vasorelaxant than SPM 3672 and produced a greater degree of tolerance. Vasorelaxation induced by GTN occurred with rapid onset and was brief, whereas SPM 3672 produced long-lasting relaxation with a more delayed onset. This kinetic pattern was confirmed in porcine coronary arteries, in which both nitrates exhibited marked relaxation, with GTN being slightly more potent than SPM 3672.(ABSTRACT TRUNCATED AT 250 WORDS)

L11 ANSWER 19 OF 20 MEDLINE on STN
ACCESSION NUMBER: 94076828 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7504767
TITLE: Endothelial and myocardial cell protection by a cysteine-containing nitric oxide donor after myocardial ischemia and reperfusion.

Searcher : Shears 571-272-2528

AUTHOR: Lefer D J; Nakanishi K; Vinten-Johansen J
CORPORATE SOURCE: Department of Cardiothoracic Surgery, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27157-1096.
SOURCE: Journal of cardiovascular pharmacology, (1993) 22 Suppl 7 S34-43.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940203
Last Updated on STN: 19960129
Entered Medline: 19940111

AB The cardioprotective actions of SPM-5185, a novel cysteine-containing nitric oxide (NO) donor, were investigated in two models of myocardial ischemia-reperfusion (MI-R) injury. In the first study, dogs were subjected to 60 min of left anterior descending (LAD) coronary artery occlusion followed by 270 min of reperfusion. During reperfusion, animals were randomly assigned to receive intracoronary SPM-5185 (500 nM) or the NO-deficient analogue of SPM-5185, SPM-5267 (500 nM). Transmural myocardial blood flow to the ischemic zone was not different between the SPM-5185 group of dogs and the SPM-5267 group (0.04 +/- 0.01 and 0.03 +/- 0.01 ml/min/g, respectively). Similarly, the area of left ventricular myocardium placed at risk by LAD coronary artery occlusion was equivalent in dogs receiving SPM-5185 (33.6 +/- 3%) and SPM-5267 (30.4 +/- 2%). However, the necrotic area, expressed as a percentage of the area at risk, was reduced by 70% in the SPM-5185-**treated** dogs (14.5 +/- 4 vs. 47.5 +/- 9%; $p < 0.001$). Furthermore, cardiac myeloperoxidase activity indicated that fewer neutrophils accumulated in the necrotic zone of the SPM-5185-**treated** dogs. In the second study, dogs were subjected to 30 min of global myocardial ischemia followed by 1 h of cardioplegic arrest and 1 h of reperfusion. SPM-5185 (10 microM) added to the blood cardioplegia solution resulted in a 95 +/- 14% post-ischemic recovery of contractile function compared with 36 +/- 8% ($p < 0.05$) in vehicle-**treated** dogs. Additionally, SPM-5185 **treatment** completely preserved coronary arterial vasorelaxation to acetylcholine after ischemia and reperfusion and resulted in a 62% reduction in cardiac tissue myeloperoxidase activity ($p < 0.05$). We conclude that (a) SPM-5185 exerts significant cardioprotection from MI-R injury after regional or global ischemia, and (b) this cardioprotection appears to be related to the inhibition of neutrophil-mediated injury.

L11 ANSWER 20 OF 20 MEDLINE on STN
ACCESSION NUMBER: 93035800 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1415601
TITLE: Beneficial effects of SPM-5185, a cysteine-containing NO donor in myocardial ischemia-reperfusion.
AUTHOR: Siegfried M R; Carey C; Ma X L; Lefer A M
CORPORATE SOURCE: Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania 19107.
CONTRACT NUMBER: GM-45434 (NIGMS)
SOURCE: American journal of physiology, (1992 Sep) 263 (3 Pt 2) H771-7.
Journal code: 0370511. ISSN: 0002-9513.

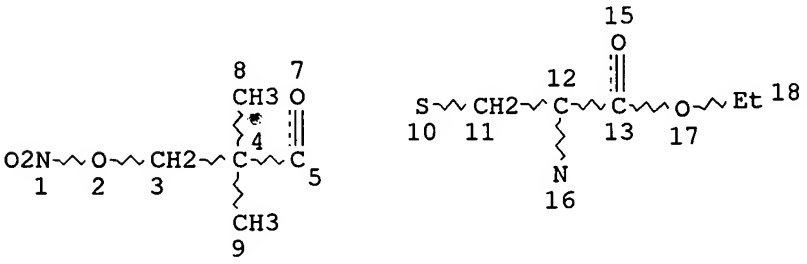
Searcher : Shears 571-272-2528

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 20000303
Entered Medline: 19921029

AB Intravenous administration of SPM-5185 [N-nitratopivaloyl-S-(N'-acetylalanyl)-cysteine ethyl ester], a cysteine-containing nitric oxide (NO) donor, or SPM-5267 [pivaloyl-S-(N'-acetylalanyl)-cysteine ethyl ester], an analogue of SPM-5185 that lacks the NO moiety, was studied in a feline myocardial ischemia-reperfusion model. Administration of SPM-5185 (1 mg/kg), followed by a 2-mg.kg-1.h-1 infusion starting 10 min before reperfusion, resulted in significant protection 4.5 h postreperfusion. In the myocardial ischemia (MI)+SPM-5267 group, 38 +/- 4% of the area at risk was necrotic, whereas the necrotic area/area at risk was only 7 +/- 2% in the MI+SPM-5185 group (P less than 0.01). Moreover, SPM-5185 **treatment** markedly attenuated the endothelial dysfunction observed in the left anterior descending coronary artery after reperfusion by 50%. These beneficial effects occurred despite the absence of a significant change in myocardial oxygen demand, as measured by the pressure-rate index. In vitro experiments demonstrated that SMP-5185, but not SPM-5267, decreased adherence of neutrophils to the coronary vascular endothelium and decreased production of superoxide radicals. Therefore, a likely mechanism of the observed cardioprotection by SPM-5185 involves attenuation of polymorphonuclear leukocyte-induced endothelial dysfunction.

(FILE 'MARPAT' ENTERED AT 12:27:38 ON 15 APR 2005)

L12 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 18
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L14 2 SEA FILE=MARPAT SSS FUL L12 (MODIFIED ATTRIBUTES)

100.0% PROCESSED 154 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L14 ANSWER 1 OF 2 MARPAT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 138:163603 MARPAT
TITLE: Methods for novel sulfur-containing organic nitrate compds. use in the treatment and prevention of human diseases and conditions
INVENTOR(S): Garvey, David S.; Letts, L. Gordon
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013432	A2	20030220	WO 2002-US24923	20020807
WO 2003013432	A3	20031113		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1414432	A2	20040506	EP 2002-786354	20020807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005501060	T2	20050113	JP 2003-518446	20020807
US 2004152753	A1	20040805	US 2004-760672	20040121
PRIORITY APPLN. INFO.:			US 2001-311715P	20010810
			WO 2002-US24923	20020807

AB The invention describes methods of use for an organic nitrate compound, or a pharmaceutically acceptable salt thereof, wherein the organic nitrate compound comprises at least one sulfur atom and/or at least one disulfide group. The invention also provides methods for treating, preventing and/or reducing inflammation, pain, and fever; for decreasing or reversing the gastrointestinal, renal and other toxicities resulting from the use of nonsteroidal antiinflammatory compds.; for treating and/or preventing gastrointestinal disorders; for treating inflammatory disease states and disorders; for treating and/or preventing ophthalmic diseases or disorders; for treating and/or improving the gastrointestinal properties of COX-2 inhibitors; for facilitating wound healing; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; for decreasing the recurrence of ulcers; for improving gastroprotective properties, anti-Helicobacter pylori properties or antacid properties of proton pump inhibitors; for treating Helicobacter pylori and viral infections. For improving gastroprotective properties of Hz receptor antagonists; for treating and/or preventing inflammations and microbial infections, multiple sclerosis, and viral infections; for treating or preventing restenosis, autoimmune diseases, pathol.

conditions resulting from abnormal cell proliferation, polycystic kidney disease, inflammatory diseases or to inhibit wound contraction; for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females; for treating or preventing benign prostatic hyperplasia, hypertension, congestive heart failure, variant (Printzmetal) angina , glaucoma, neurodegenerative disorders, vasospastic diseases, cognitive disorders, urge incontinence, and overactive bladder; for reversing the state of anesthesia. For treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP); for treating respiratory disorders and for treating neurol. conditions.

L14 ANSWER 2 OF 2 MARPAT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 123:199401 MARPAT
TITLE: Preparation of amino acid disulfide cardiovascular agents and vasodilators
INVENTOR(S): Sandrock, Klaus; Feelisch, Martin; Boekens, Hilmar
PATENT ASSIGNEE(S): Schwarz Pharma AG, Germany
SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4321306	A1	19950105	DE 1993-4321306	19930626
WO 9500477	A1	19950105	WO 1994-DE726	19940624
W: CA, CN, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 705244	A1	19960410	EP 1994-918734	19940624
EP 705244	B1	19981104		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1126466	A	19960710	CN 1994-192601	19940624
CN 1045594	B	19991013		
JP 08511777	T2	19961210	JP 1994-502335	19940624
AT 172963	E	19981115	AT 1994-918734	19940624
ES 2126122	T3	19990316	ES 1994-918734	19940624
CA 2165992	C	20000822	CA 1994-2165992	19940624
US 5661129	A	19970826	US 1995-557106	19951205
HK 1013283	A1	20000519	HK 1998-114613	19981222
PRIORITY APPLN. INFO.:			DE 1993-4321306	19930626
			WO 1994-DE726	19940624

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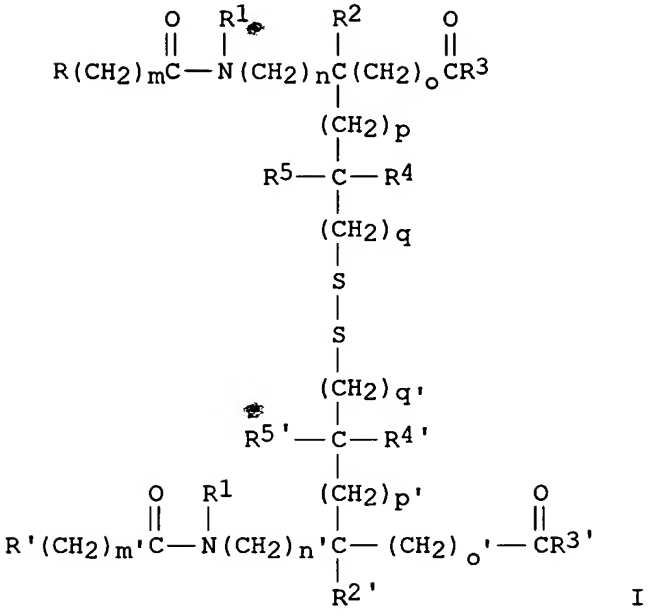
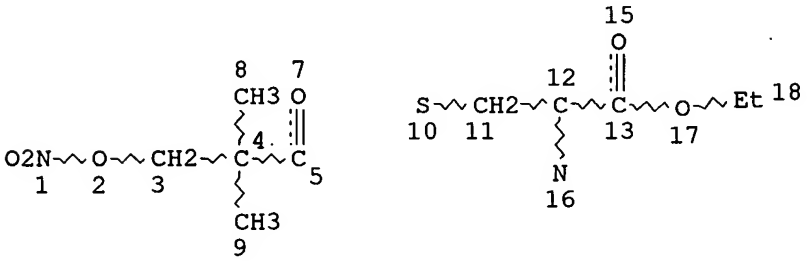


I

AB The title compds. [I; R, R' = (un)substituted nitratoalkyl, (un)substituted Ph; R1, R1', R4, R4', R5, R5' = H, lower alkyl; R2, R2' = H, (un)substituted lower alkyl, Ph, methoxyphenyl, etc.; R3, R3' = HO, lower alkenoxy, (un)substituted lower alkoxy, (un)substituted aryloxy, etc; m, m', n, n', p, p', q, q' = 0-10] [e.g., N,N'-di(3-nitratopivaloyl)-L-cystine di-Et ester (II)], useful as cardiovascular agents and vasodilators, are prepared and a I-containing formulation presented. II was prepared and demonstrated a EC50 for 50% dilation of excised rat aorta rings of 1.5 x 10-6 M.

FILE 'MARPATPREV' ENTERED AT 12:28:38 ON 15 APR 2005

L12 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 18
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:29:11 ON 15 APR 2005)

Author(s)

L16 663 S "GARVEY D"?/AU
L17 588 S ("LETTS L"? OR "LETTS G"?)/AU
L18 141 S L16 AND L17

L31 0 SEA ABB=ON PLU=ON (L16 OR L17 OR L18) AND (NITRATOPIVALOYL OR NITRATO PIVALOYL)
L32 30 SEA ABB=ON PLU=ON (L16 OR L17 OR L18) AND (TREAT? OR THERAP? OR PREVENT?)(5A)((PEPTIC OR GASTRODUODEN? OR GASTR? DUODEN? OR MARGINAL)(5A) UCLER? OR (GASTROINTESTIN? OR GASTR? INTESTIN? OR INTESTIN? OR GASTR## OR STOMACH)(5A) (DISORDER OR DISEAS?))
L33 24 DUP REM L32 (6 DUPLICATES REMOVED)

L33 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:41217 CAPLUS
DOCUMENT NUMBER: 140:111135
TITLE: Preparation of nitrosated nonsteroidal antiinflammatory compounds
INVENTOR(S): Earl, Richard A.; Ezawa, Maiko; Fang, Xinqin; **Garvey, David S.**; Gaston, Ricky D.; Khanapure, Subhash P.; **Letts, Gordon L.**; Lin, Chia-En; Ranatunge, Ramani R.; Richardson, Stewart K.; Schroeder, Joseph D.; Stevenson, Cheri A.; Wey, Shiow-Jyi
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004648	A2	20040115	WO 2003-US21026	20030703
WO 2004004648	A3	20041028		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004024057	A1	20040205	US 2003-612014	20030703

PRIORITY APPLN. INFO.:

US 2002-393111P	P	20020703
US 2002-397979P	P	20020724
US 2002-418353P	P	20021016
US 2003-449798P	P	20030226

US 2003-456182P P 20030321

OTHER SOURCE(S): MARPAT 140:111135
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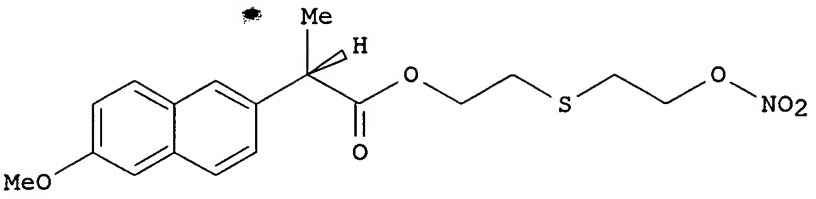


II

AB Title compds. RnRmHC-CO-X [Rm = H, alkyl; Rn = 4-((thiophen-2-yl)carbonyl)phenyl, 3-(benzoyl)phenyl, etc.; X = Y-alkyl-aryl, etc.; Y = O, S; I] are prepared For instance, naproxen is coupled to 2,2'-thiodiethanol (CH2Cl2, DMAP, EDCI) and treated with Ac2O/HNO3 at 0° to give II. I are nitrosated nonsteroidal antiinflammatory drugs (NSAIDs) used alone or are combined with one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase. The invention provides methods for **treating** inflammation, pain, fever, **gastrointestinal disorders**, etc.

L33 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:100820 CAPLUS
DOCUMENT NUMBER: 140:163865
TITLE: Preparation of nitrosated (pyridylmethylsulfinyl)benzimidazolecarboxylate derivatives as proton pump inhibitors
INVENTOR(S): Fang, Xinqin; **Garvey, David S.**; **Letts, L. Gordon**
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 47 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004024014	A1	20040205	US 2003-631782	20030801
WO 2004012659	A2	20040212	WO 2003-US23963	20030801
WO 2004012659	A3	20041007		

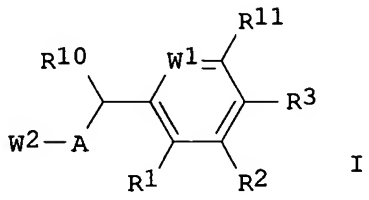
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-399715P P 20020801

OTHER SOURCE(S): MARPAT 140:163865

GI



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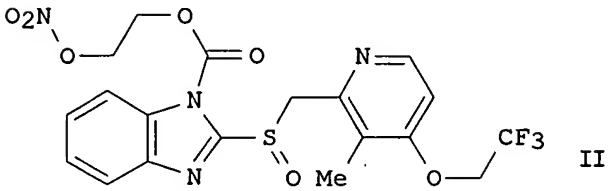

II

AB Title compds. I (12 addnl. Markush structures), [wherein R1 = H, alkoxy, alkyl, alkylthio; R2 = H, halogen, (halo)alkoxy, (alkoxy)alkyl, alkylthio, amino, or R2 and R3 taken together with the carbon atoms to which they are attached form a cycloalkyl ring, aryl, or heterocyclic ring; R3, R11 = independently H, alkoxy, alkyl, alkylthio, or R3 and R11 taken together with the carbon chain to which they are attached form cycloalkyl ring, aryl, or heterocyclic ring; R10 = H or R10 and R1 taken together with the carbon chain to which they are attached form cycloalkyl ring; A = SOn, n = 0-2; W1 = CH, N, amino-substituted carbon; W2 = (un)substituted (aza)benzimidazole, 1-phenylimidazolyl, 1-(2-pyridinyl)imidazolyl, thieno[3,4-d]imidazolyl; and pharmaceutically acceptable salts thereof], were prepared as proton pump inhibitors. For example, reaction of lansoprazole with 2-(nitrooxy)ethyl chloroformate in the presence of NaH in THF at 0 °C gave II in 62%. Thus, I and their pharmaceutical compns. are useful as proton pump inhibitors, that donate, transfer or release nitric oxide, stimulate endogenous synthesis of nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor or are the substrate for nitric oxide synthase. The invention also also provide for novel kits comprising at least one nitrosated proton pump inhibitor compound, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. Furthermore, I and their pharmaceutical compns. are also useful for the **treatment** of **gastrointestinal disorders**; facilitating ulcer healing; decreasing the recurrence of ulcers; improving gastroprotective properties, anti-Helicobacter pylori properties or antacid properties of proton pump inhibitors; decreasing or reducing the gastrointestinal toxicity associated with the use of nonsteroidal antiinflammatory compds.; and treating bacterial infections and/or viral infections (no data).

L33 ANSWER 3 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-226286 [21] WPIDS
DOC. NO. CPI: C2004-089176
TITLE: New nitrosated and/or nitrosylated cyclooxygenase inhibiting compounds used for treating e.g. inflammation, pain, fever and gastrointestinal disorders.
DERWENT CLASS: B02 B03 B05
INVENTOR(S): **GARVEY, D S**; KHANAPURE, S P; RANATUNGE, R R; RICHARDSON, S K; SCHROEDER, J D
PATENT ASSIGNEE(S): (NITR-N) NITROMED INC
COUNTRY COUNT: 105
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004010945	A2	20040205	(200421)*	EN	140
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2004072883	A1	20040415	(200426)		
AU 2003261281	A1	20040216	(200453)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004010945	A2	WO 2003-US23605	20030729
US 2004072883	A1 Provisional	US 2002-398829P	20020729
		US 2003-628375	20030729
AU 2003261281	A1	AU 2003-261281	20030729

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003261281	A1 Based on	WO 2004010945

PRIORITY APPLN. INFO: US 2002-398829P 20020729; US 2003-628375 20030729

AN 2004-226286 [21] WPIDS

AB WO2004010945 A UPAB: 20040326
NOVELTY - Nitrosated and/or nitrosylated cyclooxygenase inhibiting compounds (I)-(VIII) are new.

DETAILED DESCRIPTION - Nitrosated and/or nitrosylated cyclooxygenase inhibiting compounds of formula (I)-(VIII) and their salts are new.

X1-Y1-Z1 = e.g. N=CR4-O, S-CR4=N or N=N-S;

R1a = H, halo, Me or CH2OH;

R2 = e.g. lower alkyl or cycloalkyl;

X5 = (CR31R32)a, (CR31R32)bb-A1, CR31R32-A1-(CR31R32), CR31= or A1;

A1 = O, thio, sulfinyl, sulfonyl or N(R33);

R31, R32 = H, optionally substituted lower alkyl, lower alkoxy, lower haloalkyl or halo, or

R31 +*R32 = oxo, thial, oxime or hydrazone;
R33 = lower alkyl, H, or COH;
a = 1 or 3;
bb = 2 or 3;
A-B' = N-C, C-N or N-N;
X2-Y2-Z2 = e.g. =N-CR4=N, =CR4-N=CR4a, =CR4-N=N or =N-N=N;
X3 = e.g. CH2-CO-Me or COH;
Y3 = e.g. Me or COH;
X6 = (CR31R32)a, (CR31R32)bb-A1 or CR31=;
X4, Z4 = N or CR21;
R21, R21a = e.g. H, lower alkyl, alkoxy, alkylthio, haloalkyl (preferably CF3), haloalkoxy (preferably fluoroalkoxy) or CN;
R20 = e.g. SO2-Me;
R22 = e.g. phenyl or pyridinyl or its N-oxide (all optionally substituted), arylalkyl or cycloalkylalkyl;
X7 = O, S, NR51, NOR52 or N-NR52R53;
Y7 = H, halo, lower alkyl, alkenyl or alkynyl;
Z7 = (CR31R32)a;
R49 = R3 or R4;
R50, R50a = e.g. H, halo, lower alkyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl;
R51 = lower alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or lower alkylheterocyclyl;
R52, R53 = lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl or heterocyclyl;
R3 = e.g. H, haloalkyl (preferably CF3), CN or lower alkyl;
X6 = (CR31R32)a, (CR31R32)bb-A1 or CR31=;
X9, Y9 = CO-U-D1 or CH2-CR5(R5a)-U-D1;
R4, R4a, R5, R5a = e.g. H, amino, CN, lower alkyl, haloalkyl, alkoxy, alkylthio, cycloalkoxy, cycloalkylthio, or phenyl or benzyl (both optionally substituted);
U = e.g. O, S;
D1 = e.g. H NO or NO2;
X10-Y10-Z10 = e.g. a group of formula (ii) or (iii);
P10 = N=, NR3, O or S;
Q10, Q10a = CR60 or N;
R60 = e.g. lower alkyl, halo (preferably CF3) or alkoxy;
A10-B10-C10-D10 = e.g. CR4=CR4a-CR5=CR5a, CR4(R4a)-CR5(R5a)-CR4(R4a)-CO or CR4(R4a)-CR5(R5a)-CO-CR4(R4a);
T = e.g. a bond, carbonyl or O;
X14 = CO or CS;
Y14 = O or S, and
A14-B14-D14 = e.g. CR4=CR4a-CR5=CR5a, CR4(R4a)-CR5(R5a)-CO or CR4(R4a)-CO-CR5(R5a),
with specified provisos.

Full definitions are given in the Definitions Field (Full Definitions).

An INDEPENDENT CLAIM is also included for a kit comprising (I)-(VIII).

ACTIVITY - Antiinflammatory; Analgesic; Antipyretic; Gastrointestinal-Gen.; Antiulcer; Antibacterial; Cytostatic; Vulnerary; Antiangiogenic; Antiarthritic; Antiasthmatic; Gynecological; Tocolytic; Dermatological; Ophthalmological; CNS-Gen.;Antiallergic; Respiratory-Gen.; Immunosuppressive; Antiarteriosclerotic; Nephrotropic; Cardiovascular-Gen.; Uropathic; Neuroprotective; Nootropic; Anticoagulant; Thrombolytic.

MECHANISM OF ACTION - Cyclooxygenase-(COX)2 inhibitor.

In an assay as described in Brideau et al, Inflamm Res, 45: 68-74 (1996) using human whole blood, results showed that

1-(1-(cyclohexylmethyl)-3-(3-(nitrooxy)propyl)pyrazol-5-yl)-4-(methylsulfonyl)benzene exhibited 90% inhibition of COX-1 and 100% inhibition of COX-2.

USE - Used for treating inflammation, pain, fever and, gastrointestinal disorders, particularly inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, peptic ulcer, stress ulcer, bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, bacterial infection, short bowel (anastomosis) syndrome,and hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia, facilitating wound healing, and treating renal and/or respiratory toxicity, angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, skin related conditions, neoplasia, inflammatory process in a disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, particularly cortical dementia, Alzheimer's disease, vascular dementia, multiinfarct dementia, pre-senile dementia, alcoholic dementia, senile dementia and central nervous system damage resulting from stroke, ischemia or trauma, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, organ deterioration, tissue deterioration, activation, adhesion and infiltration of neutrophils at the site of inflammation (all claimed).

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L33 ANSWER 4 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-203371 [19] WPIDS
DOC. NO. CPI: C2004-080049
TITLE: New oxime and/or hydrazone containing nitrosated and/or nitrosylated derivatives are cyclooxygenase 2 selective inhibitors useful to **treat** inflammation, **gastrointestinal disorder**, pain and fever.
DERWENT CLASS: B05
INVENTOR(S): **GARVEY, D S**; RANATUNGE, R R; RICHARDSON, S K
PATENT ASSIGNEE(S): (NITR-N) NITROMED INC
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004002420	A2	20040108	(200419)*	EN	166
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2004006133	A1	20040108	(200419)		
AU 2003279622	A1	20040119	(200447)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2004002420	A2	WO 2003-US20421	20030630
US 2004006133	A1 Provisional	US 2002-392044P	20020628
		US 2003-608333	20030630
AU 2003279622	A1	AU 2003-279622	20030630

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003279622	A1 Based on	WO 2004002420

PRIORITY APPLN. INFO: US 2002-392044P 20020628; US 2003-608333 20030630

AN 2004-203371 [19] WPIDS

AB WO2004002420 A UPAB: 20040326

NOVELTY - Oxime and/or hydrazone containing nitrosated and/or nitrosylated derivatives (I)-(XVI) are new.

DETAILED DESCRIPTION - Oxime and/or hydrazone containing nitrosated and/or nitrosylated derivatives of formula (I)-(XVI) and their salts are new.

Full Definitions are given in the DEFINITION (Full Definitions) section.

An INDEPENDENT CLAIM is also included for a kit comprising at least one compound (I)-(XVI).

ACTIVITY - Antiinflammatory; Analgesic; Antipyretic; Gastrointestinal-Gen.; Nephrotropic; Respiratory-Gen.; Anticoagulant; Thrombolytic; Vulnerary; Antiulcer; Tranquilizer; Hemostatic; Antibacterial; Cytostatic.; Antiangiogenic; Antiarthritic; Antiasthmatic; Gynecological; Tocolytic; Ophthalmological; CNS-Gen.; Antiallergic; Immunosuppressive; Antiarteriosclerotic; Antimicrobial; Cardiovascular-Gen.; Uropathic; Dermatological;. Nootropic; Cerebroprotective; Vasotropic; Neuroprotective.

MECHANISM OF ACTION - Cyclooxygenase 2 (COX-2) Inhibitor.

In a COX-2 inhibitory assay in humans using the method of Bridean et al, Inflamm Res., 45: 68-74 (1996), 1-(3-(2-aza-2-methoxy-1-(3-(nitrooxy)propyl)vinyl)-1-cyclohexylpyrazo-5-yI)-4-(methylsuIfonyl)benzene at 1 micro M inhibited COX-2 by 55 %.

USE - Compounds (I)-(XVI) are useful to treat or reduce inflammation, pain or fever, gastrointestinal disorder (preferably an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, peptic ulcer, stress ulcer, bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, bacterial infection, short-bowel (anastomosis) syndrome, or hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia), improving the gastrointestinal properties of COX-2 inhibitor, treat or reverse renal and/or respiratory toxicity, disorder resulting from elevated levels of COX-2(angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia, an inflammatory process in a disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, organ deterioration, tissue deterioration, or activation, adhesion and infiltration of neutrophils at the site of inflammation, neoplasia(brain cancer, bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma,

gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamous cell cancer, basal cell cancer, prostate cancer, renal cell carcinoma, cancerous tumor, growth, polyp, adenomatous polyp, familial adenomatous polyposis or fibrosis resulting from radiation therapy),central nervous system disorder (cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, or central nervous system damage resulting from stroke, ischemia or trauma). The compounds also inhibit platelet aggregation and facilitate wound healing (ulcer) (all claimed).

ADVANTAGE - The compounds have gastroprotective properties, facilitate wound healing, decreased renal toxicity and dyspepsia, improved cardiovascular profile and can be used in lower dosage.

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L33 ANSWER 5 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-191037 [18] WPIDS

DOC. NO. CPI: C2004-075269

TITLE: New 5-aryl pyrazole derivatives and 4-aryl isoxazole derivatives are cyclooxygenase-2 selective inhibitor useful for treating elevated level of COX-2 disorders e.g. angiogenesis, arthritis and endothelial dysfunction.

DERWENT CLASS: B02 B03

INVENTOR(S): BANDARAGE, U K; EARL, R A; EZAWA, M; FANG, X; **GARVEY, D S**; KHANAPURE, S P; RANATUNGA, R R; RICHARDSON, S K; SCHROEDER, J D; STEVENSON, C A; WEY, S; RANATUNGE, R R

PATENT ASSIGNEE(S): (NITR-N) NITROMED INC

COUNTRY COUNT: 102

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004002409	A2	20040108	(200418)*	EN	116

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

US 2004053985	A1	20040318	(200421)		
AU 2003247622	A1	20040119	(200447)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2004002409	A2		WO 2003-US19850	20030625
US 2004053985	A1	Provisional	US 2002-391769P	20020627
		Provisional	US 2003-454307P	20030314
			US 2003-603098	20030625
AU 2003247622	A1		AU 2003-247622	20030625

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003247622	A1 Based on	WO 2004002409

PRIORITY APPLN. INFO: US 2003-454307P 20030314; US 2002-391769P 20020627; US 2003-603098 20030625

AN 2004-191037 [18] WPIDS

AB WO2004002409 A UPAB: 20040316

NOVELTY - 5-aryl pyrazole derivatives (I), (II) and 4-aryl isooxazole derivatives (III) are new.

DETAILED DESCRIPTION - 5-aryl pyrazole derivatives of formula (I), (II) and 4-aryl isooxazole derivatives of formula (III) are new.

INDEPENDENT CLAIMS are also included for

(1) a composition (A) comprising (I), (II) and (III) and a carrier;

(2) a composition (B) comprising at least one of (I), (II) or (III) and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase(C); and

(3) a kit comprising at least one of (I), (II) or (III).

R1 = -S(O)2-CH3 or -S(O)2-NH2;

R'1 = H, halo, methyl or CH2OH;

R2 = substituted lower alkyl, cycloalkyl, aryl or a heterocyclic ring;

R3 =*-(C(R4)(R'4))k-Y-(C(R4)(R'4))n-O-V, -C(Z)-(C(R4)(R'4))k-O-V, -C(Z)-(C(R4)(R'4))k-Y-(C(R4)(R'4))n-O-V, -(C(R4)(R'4))k-Y-(C(R4)(R'4))n-C(Z)-(C(R4)(R'4))n-O-V, -(C(R4)(R'4))k-CH=CH-(C(R4)(R'4))p-O-V, -(C(R4)(R'4))n-O-V, -(C(R4)(R'4))n-W-Q-(C(R4)(R'4))k-0-V, -C(Z)-W-Q-(C(R4)(R'4))k-O-V, -C(O)-N(Ri)-O-(C(R4)(R'4)n-O-V, -(C(R4)(R'4))k-C equivalent to C-(C(R4)(R'4))P-O-V, -(C(R4)(R'4))k-Y-(C(R4)(R'4))k-Y-(C(R4)(R'4))k-O-V, -(C(R4)(R'4))p-E-N(Ri)-O-W-Q-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) p-E-N(Ri)-O-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) p-N(Ri)-O-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) p-O-N(Ri)-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) P-O-N(Ri)-E-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) P- O-N(Ri)-E-W-Q-(C(R4)(R'4) k-0-V, -(C(R4)(R'4)) P-C(Z)-Y-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) p-Y-C(Z)-(C(R4)(R'4) k-O-V or -(C(R4)(R'4)) p-Y-C(Z)-Y-(C(R4)(R'4) k-O-V;

Either R4, R'4 = H, halo, lower alkyl or alkoxy; or

CR4R'4 = a substituted lower alkyl, a cycloalkyl, aryl or a heterocyclic ring;

V = -NO, -NO2, or H;

Y = O,-S(O) o- or -N(Ra)R-;

Z = oxo, thial, oxime or hydrazone;

Q = Y or a covalent bond;

W = aryl, alkylaryl, heterocyclic ring or alkyl heterocyclic ring;

E = -C(O) or -S(O) o;

Ra = a lone pair of electron, a hydrogen or a lower alkyl group;

Ri = H, alkyl, aryl, alkyl carboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, arylcarboxylic ester, alkylcarboxamido, arylcarboxamido, an alkylaryl, alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyl, arylsulfonyloxy, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, -(C(R4)(R'4)) n-O-V, a bond to an adjacent atom creating a double bond to that atom or -(N2O2-)-.M+;

M+ = an organic or inorganic cation;

o = 0-2;
k = 1-6;
p = 0-10;
n = 2-10;

R5 = -(C(R4)(R'4)) k-Y-(C(R4)(R'4)) k-B-(C(R4)(R'4)) k-O-V, -(C(R4)(R'4)) k-Y-(C(R4)(R4)) k-D-(C(R4)(R'4)) k-O-V, -C(Z)-(C(R4)(R'4)) k-Y-(C(R4)(R'4)) k-O-V, -(C(R4)(R'4)) k-Y-W-Q-C(R4)(R'4)) k-O-V, -C(Z)-W-Q-(C(R4)(R'4)) k-O-V, -(C(R4)(R'4)) p-E-N(Ri)-O-W-Q-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) p-E-N(Ri)-O-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) p-N(Ri)-O-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) p-O-N(Ri)-(C(R4)(R'4) k-O-V, -(C(R4)(R'4)) P-O-N(Ri)-E-(C(R4)(R'4) k-O-V or-(C(R4)(R'4)) p- O-N(Ri)-E-W-Q-(C(R4)(R'4) k-O-V;

B = -C(Z)-, -Y- or a covalent bond; and

D = - S(O)o or -N(Ra)(Rj).

Provided that when R2 is cycloalkyl, aryl or a heterocyclic ring, R3 cannot be -(C(R4)(R'4)) n-O-V, where R4 and R'4 at each occurrence are independently H, halo, lower alkyl or alkoxy and V is H.

ACTIVITY - Antiinflammatory; Analgesic; Antipyretic; Gastrointestinal -Gen.; Antiulcer; Tranquilizer; Antibacterial; Cytostatic; Antiangiogenic; Antiarthritic; Antiasthmatic; Gynecological; Tocolytic; Dermatological; Ophthalmological; CNS-Gen.; Nootropic; Cerebroprotective; Vasotropic; Vulnerary; Antiallergic; Respiratory-Gen.; Antiarteriosclerotic; Antimicrobial; Cardiovascular-Gen.; Uropathic; Nephrotropic; Hemostatic; Neuroprotective; Anticoagulant; Thrombolytic. (I), (II) and (III) was tested for their COX-2 inhibitor activity in human using Brideau et al., Inflamm Res., 45: 68-74 (1996) . The results showed that the percentage inhibition of 4-(1-(4-Methoxyphenyl)-3-((3-nitrooxy)propoxy)methyl)pyrazol-5-yl)-1-(methylsulfonyl)benzene at 10 micro M was 100%.

MECHANISM OF ACTION - Cyclooxygenase-2 selective (COX-2) inhibitor.

USE - (I), (II) or (III) is useful for treating or reducing inflammation, pain or fever. Also useful for treating or reversing renal or respiratory toxicity. Also useful for inhibiting platelet aggregation and also for facilitating wound (ulcer) healing. Also useful for treating a gastrointestinal disorder (e.g. an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia) or improving the gastrointestinal properties of a COX-2 inhibitor and disorders resulting from elevated levels of COX-2 (e.g. angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia(e.g. a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy), an inflammatory process in a disease, an ophthalmic disorder, pulmonary inflammation, a central

nervous system disorder(e.g. cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, or central nervous system damage resulting from stroke, ischemia or trauma), allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, a microbial infection, a cardiovascular disorder, a urinary disorder, a urological disorder, endothelial dysfunction, organ deterioration, tissue deterioration, or activation, adhesion and infiltration of neutrophils at the site of inflammation)(All claimed).

ADVANTAGE - (I), (II) and (III) have gastroprotective properties, facilitate wound healing, decreased renal toxicity and dyspepsia, improved cardiovascular profile and that can be used at low dosages.

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L33 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:132965 CAPLUS
DOCUMENT NUMBER: 138:163603
TITLE: Methods for novel sulfur-containing organic nitrate compds. use in the treatment and prevention of human diseases and conditions
INVENTOR(S): **Garvey, David S.; Letts, L. Gordon**
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013432	A2	20030220	WO 2002-US24923	20020807
WO 2003013432	A3	20031113		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1414432	A2	20040506	EP 2002-786354	20020807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005501060	T2	20050113	JP 2003-518446	20020807
US 2004152753	A1	20040805	US 2004-760672	20040121
PRIORITY APPLN. INFO.:			US 2001-311715P P	20010810
			WO 2002-US24923 W	20020807

OTHER SOURCE(S): MARPAT 138:163603

AB The invention describes methods of use for an organic nitrate compound, or a pharmaceutically acceptable salt thereof, wherein the organic nitrate compound comprises at least one sulfur atom and/or at least one disulfide group. The invention also provides methods for treating, preventing and/or reducing inflammation, pain, and fever; for

decreasing or reversing the gastrointestinal, renal and other toxicities resulting from the use of nonsteroidal antiinflammatory compds.; for **treating** and/or **preventing gastrointestinal disorders**; for **treating** inflammatory **disease** states and disorders; for **treating** and/or preventing ophthalmic diseases or disorders; for treating and/or improving the gastrointestinal properties of COX-2 inhibitors; for facilitating wound healing; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; for decreasing the recurrence of ulcers; for improving gastroprotective properties, anti-Helicobacter pylori properties or antacid properties of proton pump inhibitors; for treating Helicobacter pylori and viral infections. For improving gastroprotective properties of Hz receptor antagonists; for treating and/or preventing inflammations and microbial infections, multiple sclerosis, and viral infections; for treating or preventing restenosis, autoimmune diseases, pathol. conditions resulting from abnormal cell proliferation, polycystic kidney disease, inflammatory diseases or to inhibit wound contraction; for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females; for treating or preventing benign prostatic hyperplasia, hypertension, congestive heart failure, variant (Printzmetal) angina , glaucoma, neurodegenerative disorders, vasospastic diseases, cognitive disorders, urge incontinence, and overactive bladder; for reversing the state of anesthesia. For treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP); for treating respiratory disorders and for treating neurol. conditions.

L33 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:836762 CAPLUS
DOCUMENT NUMBER: 139:350474
TITLE: Preparation and compositions of nitrosothio (hetero)cyclic nitric oxide donors
INVENTOR(S): Fang, Xinqin; **Garvey, David S.**; Gaston, Ricky D.; Lin, Chia-en; Ranatunga, Ramani R.; Richardson, Stewart K.; Wang, Tiansheng; Wang, Weiheng; Wey, Shiow-jyi
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003086282	A2	20031023	WO 2003-US10562	20030407
WO 2003086282	A3	20040429		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,

SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2480832	AA	20031023	CA 2003-2480832	20030407
US 2003203915	A1	20031030	US 2003-407420	20030407
EP 1497268	A2	20050119	EP 2003-719621	20030407

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.: US 2002-369873P P 20020405

WO 2003-US10562 W 20030407

OTHER SOURCE(S): MARPAT 139:350474

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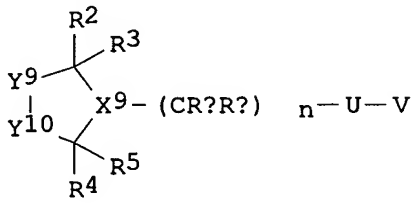
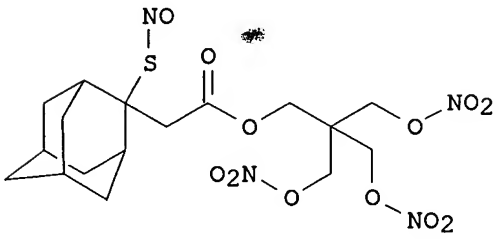


I



II

AB Title compds. I [wherein U = O, S, or NRaRi; V = NO or NO2; X9 = CR10 or N; Y9 = CR6R7, NRi, NR25, NRiCR6R7, CR6R7NRi, CR2R3CR6R7, or CR6R7CR2R3; Y10 = CR8R9 or CR8R9CR17R18; R2-R9, R17, and R18 = independently H or alkyl; or R2R3, R4R5, R6R7, or R8R9 = independently oxo; or R4 and R7 together with the C's to which they are attached = cycloalkyl; or CR6R7 = cycloalkyl; R6 and R9 taken together with the C's to which they are attached = (bridged)cycloalkyl, heterocyclyl, or aryl with the proviso that R7 and R8 are not present; R4 and R25 taken together with the C and N to which they are attached = heterocyclyl; Ra = lone pair of electrons, H, or (aryl)alkyl; Re and Rf = independently H, halo, OH, or (un)substituted (cyclo)alkyl, heterocyclyl, alkoxy, amino, aryl, etc.; or CReRf = heterocyclyl or (bridged) cycloalkyl; Ri = H or (un)substituted alkyl, aryl, carboxamido, sulfonamido, etc.; n = 0-3; and pharmaceutically acceptable salts thereof] were prepared as novel nitric oxide donors for use in compns. comprising at least one nitric oxide donor and optionally at least one therapeutic agent. The nitric oxide donors donate, transfer or release nitric oxide, and/or elevate endogenous levels of endothelium-derived relaxing factor, and/or stimulate endogenous synthesis of nitric oxide and/or are substrates for nitric oxide synthase and are capable of releasing nitric oxide or indirectly delivering or transferring nitric oxide to targeted sites under physiol. conditions (no data). For example, 2-[2-(nitrosothio)adamantan-2-yl]acetic acid was esterified with

3-nitrooxy-2,2-bis(nitrooxymethyl)propan-1-ol in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide•HCl and 4-dimethylaminopyridine in CH2Cl2 to give II (18%). The latter inhibited proliferation of human coronary artery smooth muscle cells with IC50 of 5 μM. In general, the nitrosylated compds. tested in this assay inhibited proliferation of vascular smooth muscle cells, while the corresponding non-nitrosylated derivs. showed no inhibition, slight inhibition, or exhibited much higher IC50 values. Thus, the invention provides methods for treating cardiovascular diseases, for the inhibition of platelet aggregation and platelet adhesion caused by the exposure of blood to a medical device, for treating pathol. conditions resulting from abnormal cell proliferation, transplantation rejections, autoimmune, inflammatory, proliferative, hyperproliferative, vascular diseases, for reducing scar tissue or for inhibiting wound contraction, particularly the prophylactic and/or therapeutic treatment of restenosis (no data). The invention also provides methods for **treating** inflammation, pain, fever, **gastrointestinal disorders**, respiratory **disorders**, and sexual dysfunctions (no data). In addition, the invention provides novel compns. and kits comprising at least one nitric oxide donor and/or at least one therapeutic agent.

L33 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:656415 CAPLUS
DOCUMENT NUMBER: 139:175861
TITLE: Nitrosated and nitrosylated phosphodiesterase inhibitor compounds for treatment of male impotence and female sexual dysfunction
INVENTOR(S): **Garvey, David S.**; De Tejada, Inigo Saenz
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 70 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003158184	A1	20030821	US 2001-24040	20011221
PRIORITY APPLN. INFO.:			US 2001-24040	20011221

OTHER SOURCE(S): MARPAT 139:175861

AB The invention provides methods for treating male impotence, female sexual dysfunctions, and anorectal diseases involving excessive anal sphincter tone by administering a therapeutically effective amount of the title inhibitor which addnl. donates, transfers, or releases NO and/or induces the production of endogenous endothelium-derived relaxing factor. Many types of phosphodiesterase inhibitors are disclosed including nitrate, nitrite, and nitrosothiol-containing derivs. of benzene, pyridine, phenol, quinoline, quinazoline, 2-pyridone, purin-6-one, purin-2,6-dione, pyrimidin-4-one, imidazo[2,1-b]quinazoline, benzo[c][1,6]naphthyridine, 2,6-dihydroxyalkyamino-4,8-dipiperidinopyrimido[5,4-d]pyrimidine, and 1-((3,4-dihydroxyphenyl)methyl)-6,7-isoquinoline. Thus, the synthesis of two such phosphodiesterase inhibitors are described. One, a nitrosothiol derivative of a 2,6-dihydroxyalkyamino-4,8-dipiperidinopyrimido[5,4-d]pyrimidine, was more effective than the phosphodiesterase inhibitor dipyridamole in relaxing contracted human corpus cavernosum tissue.

L33 ANSWER 9 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:366697 BIOSIS
DOCUMENT NUMBER: PREV200300366697
TITLE: Nitrosated and nitrosylated nonsteroidal antiinflammatory compounds, compositions and methods of use.
AUTHOR(S): Bandarage, Upul K. [Inventor, Reprint Author]; Dong, Qing [Inventor]; Fang, Xinqin [Inventor]; **Garvey, David S.** [Inventor]; Mercer, Gregory J. [Inventor]; Richardson, Stewart K. [Inventor]; Schroeder, Joseph D. [Inventor]; Wang, Tiansheng [Inventor]
CORPORATE SOURCE: Newton, MA, USA
ASSIGNEE: NitroMed, Inc.
PATENT INFORMATION: US 6593347 July 15, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 15 2003) Vol. 1272, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

AB The present invention describes novel nitrosated and/or nitrosylated nonsteroidal antiinflammatory compounds, and novel compositions comprising at least one nitrosated and/or nitrosylated nonsteroidal antiinflammatory compound, and, optionally, at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. The present invention also provides methods for treating, preventing and/or reducing inflammation, pain, and fever; decreasing or reversing the gastrointestinal, renal and other toxicities resulting from the use of nonsteroidal antiinflammatory drugs; **treating** and/or **preventing gastrointestinal disorders**; **treating** inflammatory **disease** states and disorders; and **treating** and/or preventing ophthalmic diseases or disorders.

L33 ANSWER 10 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:239203 BIOSIS
DOCUMENT NUMBER: PREV200300239203
TITLE: H2 receptor antagonist compounds in combination with nitric oxide donors, compositions and methods of use.
AUTHOR(S): **Garvey, David S.** [Inventor, Reprint Author]; **Letts, L. Gordon** [Inventor]; Wang, Tiansheng [Inventor]
CORPORATE SOURCE: ASSIGNEE: NitroMed, Inc.
PATENT INFORMATION: US 6552047 April 22, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Apr 22 2003) Vol. 1269, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 14 May 2003

Searcher : Shears 571-272-2528

Last Updated on STN: 14 May 2003

AB The present invention describes novel nitrosated and/or nitrosylated H2 receptor antagonist compounds, and novel compositions comprising at least one H2 receptor antagonist compound that is optionally substituted with at least one NO and/or NO2 group, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase. The present invention also describes methods for **treating** and/or **preventing** **gastrointestinal disorders**; improving gastroprotective properties of H2 receptor antagonists; decreasing the recurrence of ulcers; facilitating ulcer healing; preventing and/or treating inflammations and microbial infections, ophthalmic diseases and disorders, multiple sclerosis, and viral infections; and decreasing or reducing the gastrointestinal toxicity associated with the use of nonsteroidal antiinflammatory compounds.

L33 ANSWER 11 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-191024 [18] WPIDS
DOC. NO. CPI: C2004-075256
TITLE: New nitrosated and/or nitrosylated compounds useful in the treatment of e.g. rheumatoid arthritis, inflammation, pain, fever, systemic lupus erythematosus and asthma.
DERWENT CLASS: B05
INVENTOR(S): **GARVEY, D S; LETTS, L G**
PATENT ASSIGNEE(S): (GARV-I) GARVEY D S; (LETT-I) LETTS L G; (NITR-N) NITROMED INC
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003103602	A2	20031218	(200418)*	EN	36
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2004072899	A1	20040415	(200426)		
AU 2003248642	A1	20031222	(200445)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003103602	A2	WO 2003-US18052	20030610
US 2004072899	A1 Provisional	US 2002-387433P	20020611
		US 2003-718060	20030610
AU 2003248642	A1	AU 2003-248642	20030610

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003248642	A1 Based on	WO 2003103602

PRIORITY APPLN. INFO: US 2002-387433P 20020611; US 2003-718060 20030610

AN 2004-191024 [18] WPIDS

AB WO2003103602 A UPAB: 20040608

NOVELTY - A nitrosated and/or nitrosylated compound (I) is new.

DETAILED DESCRIPTION - Nitrosated and/or nitrosylated compounds of formula (I) and their salts are new.

R4 = Me or Et;

R5 = Cl or F;

R6, R8 = H or F;

R7 = H, F, Cl, CH3, C2H5, OMe, OEt or OH;

R9 = Cl, F, CF3 or Me;

X = O, S(O)o or N(Ra)Ri;

K' = -Wa-Eb-(C(Re)(Rf))p-Ec-(C(Re)(Rf))x-Wd-(C(Re)(Rf))y-Wi-Ej-Wg-(C(Re)(Rf))z-T-Q (a1) or -Wa-Eb-(C(Re)(Rf))p-Ec-(C(Re)(Rf))x-Wd-(C(Re)(Rf))y-Wi-Ej-Wg-(C(Re)(Rf))z-R3 (b1);

R3 = -X-C(O)-CH2-phenyl (substituted at 5-position by R4 and on 2-position by T');

T' = -NH-phenyl (penta-substituted at 2-6 positions by R5-R9 respectively);

Q = NO or NO2;

a, b, c, d, g, i, j = 0-3;

p, x, y, z = 0-10;

W = C(O), C(S), T, (C(Re)(Rf))h, alkyl, aryl, (aryl)heterocyclic ring or (CH2CH2O)q;

E = T, alkyl, aryl, (C(Re)(Rf))h, (aryl)heterocyclic ring or (CH2CH2O)q;

h = 1-10;

q = 1-5;

Re, Rf = U, alkylaryl, alkylcycloalkyl, alkylheterocyclic, cycloalkylthio, cycloalkenyl, alkylaryl, sulfonic ester, phosphoryl, Wh, T-Q or -(C(Rg)(Rh))k-T-Q; or

CReRf = carbonyl, methanthial, heterocyclic ring, cycloalkyl, aryl, oxime, hydrazone or bridged cycloalkyl;

U = H, alkyl, cycloalkoxy, halo, OH, hydroxyalkyl, alkoxyalkyl, arylheterocyclic, cycloalkylalkyl, heterocyclicalkyl, (halo)alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkoxyhaloalkyl, sulfonic acid, sulfonic ester, alkylsulfonic acid, arylsulfonic acid, arylalkoxy, alkylthio, arylthio, CN, aminoalkyl, aminoaryl, aryl, arylalkyl, (alkyl)carboxamido, arylcarboxamido, amidyl, carboxyl, carbamoyl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarbonyl, arylcarbonyl, ester, carboxylic ester, alkylcarboxylic ester, arylcarboxylic ester, sulfonamido, alkylsulfonamido, arylsulfonamido, alkylsulfonyl, alkylsulfonyloxy, arylsulfonyl, arylsulfonyloxy, urea or nitro;

Rg, Rh = Re;

k = 1-3;

T = covalent bond, carbonyl, O, S(O)o or N(Ra)Ri;

o = 0-2;

Ra = lone pair of electrons, H or alkyl;

Ri = U', -CH2-C(T-Q)(Re)(Rf)-, a bond to adjacent atom creating double bond to that atom or -(N2O2)-.M+;

M+ = organic or inorganic cation;

U' = H, alkyl, aryl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarboxylic ester, arylcarboxylic ester, alkylcarboxamido, arylcarboxamido, alkylaryl, alkylsulfinyl, alkylsulfonyl, alkylsulfonyloxy, arylsulfinyl, arylsulfonyl, arylsulfonyloxy,

sulfonamido, carboxamido, carboxylic ester, aminoalkyl or aminoaryl; provided that:

(i) at least one Re is -T-Q or -(C(Rg)(Rh))k-T-Q when K' is (b1) and X-K' does not include nitroxyl lower alkyl ester; and

(ii) the nitrosated and/or nitrosylated compound (I) must contain at least one NO or NO2 group linked to (I) through O, N or S.

INDEPENDENT CLAIMS are also included for:

(1) a composition (III) comprising (I) and at least one compound (b) that donates, transfers or releases nitric oxide or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase;

(2) a kit (A) comprising (I) or its salt;

(3) a kit (B) comprising (II) or (III); and

(4) a kit (C) comprising at least one parent cyclooxygenase (COX)-2 inhibitor (a) and at least one compound (b) or at least one therapeutic agent.

ACTIVITY - Antiinflammatory; Analgesic; Antipyretic; Gastrointestinal-Gen.; Antiulcer; Antibacterial; Vulnerary; Respiratory-Gen.; Antiangiogenic; Antiarthritic; Gynecological; Tocolytic; Dermatological; Cytostatic; Ophthalmological; CNS-Gen.; Nootropic; Neuroprotective; Cerebroprotective; Vasotropic; Tranquilizer; Antiallergic; Antibacterial; Antiarteriosclerotic; Virucide; Cardiovascular-Gen.; Uropathic; Anticoagulant; Thrombolytic; Osteopathic; Antigout.

No biological data given.

MECHANISM OF ACTION - Platelet aggregation inhibitor; Activation, adhesion and infiltration of neutrophils inhibitor; Cyclooxygenase-2 (COX-2) inhibitor; Endogenous NO stimulator.

USE - For treating or reducing inflammation, pain, fever, gastrointestinal disorders e.g. inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, peptic ulcer, stress ulcer, bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, bacterial infection, short-bowel (anastomosis) syndrome and hypersecretory state associated with systemic mastocytosis, basophilic leukemia and hyperhistaminemia; for improving gastrointestinal properties of COX-2 inhibitor; for facilitating wound healing e.g. ulcer; for treating or reversing renal and/or respiratory toxicity, disorder resulting from elevated levels of cyclooxygenase-2 (COX-2) e.g. angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, skin-related condition, neoplasia (e.g. brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamous cell cancer, basal cell cancer, prostate cancer, renal cell carcinoma, cancerous tumor, growth, polyp, adenomatous polyp, familial adenomatous polyposis and fibrosis resulting from radiation therapy), inflammatory processes in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorders (e.g. cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, central nervous system damage resulting from stroke, ischemia and trauma), allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation and/or microbial infection, cardiovascular disorder, urinary and/or urological disorder, endothelial dysfunction, preservation of organs and tissues; for

inhibition of activation, adhesion and infiltration of neutrophil at the site of inflammation; for inhibition of platelet aggregation (claimed); for treating degenerative diseases e.g. osteoarthritis, systemic lupus erythematosus, symptoms associated with influenza and other viral infections, common cold, dysmenorrhea, headache, myositis, neuralgia gout arthritis, and spondyloarthropathies.

ADVANTAGE - The compound is potent cyclooxygenase 2 selective inhibitor. The compound exhibits gastroprotective properties; facilitates wound healing; decreases renal and/or respiratory toxicity and dyspepsia; improves cardiovascular profile and hence can be used as low dosage. The compound stimulates endogenous NO or elevated levels of endogenous endothelium-derived relaxing factor in vivo or are substrate for nitric oxide synthase.

Dwg.0/0

L33 ANSWER 12 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-021519 [02] WPIDS
CROSS REFERENCE: 2000-399322 [34]; 2002-048251 [06]; 2002-225943 [28]
DOC. NO. CPI: C2004-006889
TITLE: Use of a composition comprising nitrosated and/or nitrosylated nonsteroidal antiinflammatory compound in the treatment of e.g. inflammation, pain and fever.
DERWENT CLASS: B03
INVENTOR(S): BANDARAGE, U K; DONG, Q; FANG, X; **GARVEY, D S**; MERCER, G J; RICHARDSON, S K; SCHROEDER, J D; WANG, T
PATENT ASSIGNEE(S): (BAND-I) BANDARAGE U K; (DONG-I) DONG Q; (FANG-I) FANG X; (GARV-I) GARVEY D S; (MERC-I) MERCER G J; (RICH-I) RICHARDSON S K; (SCHR-I) SCHROEDER J D; (WANG-I) WANG T
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003207919	A1	20031106	(200402)*		60

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2003207919	A1	CIP of	US 1998-182433	19981030
		Div ex	US 1999-429019	19991029
		Div ex	US 2001-938560	20010827
			US 2003-431457	20030508

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 2003207919	A1	Div ex	US 6297260
		Div ex	US 6593347

PRIORITY APPLN. INFO: US 1999-429019 19991029; US 1998-182433 19981030; US 2001-938560 20010827; US 2003-431457 20030508
AN 2004-021519 [02] WPIDS

Searcher : Shears 571-272-2528

CR 2000-399322 [34]; 2002-048251 [06]; 2002-225943 [28]
AB US2003207919 A UPAB: 20040107
NOVELTY - Treatment, prevention or reduction of inflammation, pain and fever involves administration of a composition comprising a carrier and at least one nitrosated and/or nitrosylated nonsteroidal antiinflammatory compound (I). (I) is selected from 50 compounds given in the specification e.g. 2-(4-methyl-4-(nitrosothio)piperidyl)ethyl 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate hydrochloride.

ACTIVITY - Analgesic; Antiinflammatory; Antipyretic; Gastrointestinal-Gen.; Antiulcer; Cytostatic; Ophthalmological; Vasotropic; Cardiant; Antirheumatic; Antiarthritic; Osteopathic; Hypotensive; Antipsoriatic; Immunosuppressive; Endocrine-Gen.; Antiemetic; Antiasthmatic; Antiarteriosclerotic; Thrombolytic; Anticoagulant; Virucide; Uropathic; Cerebroprotective; Vulnerary; Tranquilizer; Hepatotropic; Immunosuppressive; Nootropic; Antidiabetic; Neuroprotective; Respiratory-Gen.; Hemostatic.

Rat paw edema test as described by Winter et al, Proc. Society Exp. Biol. Med. 111:544 - 547, 1962 was used to detected the antiinflammatory activity of 2-(4-methyl-4-(nitrosothio)piperidyl)ethyl 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate hydrochloride (A). (A) showed an activity of 1.2 as compared to Diclofenac which showed an activity of 1.

MECHANISM OF ACTION - Phenylbenzoquinone-induce writhing inhibitor.

USE - In the treatment, prevention or reduction of inflammation, pain, fever; for treating or reversing gastrointestinal, renal or other toxicity; for **treating** or **preventing** **gastrointestinal disorder** (e.g. peptic ulcer, **gastric** hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, stress ulcer, bleeding peptic ulcer, short bowel syndrome and hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia) and ophthalmic disease or disorder (e.g. glaucoma, inflammation of the eye and elevation of intraocular pressure); for treating an inflammatory disease or disorder (e.g. reperfusion injury to an ischemic organ, myocardial infarction, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, hypertension, psoriasis, organ transplant rejection, organ preservation, female or male sexual dysfunction, radiation-induced injury, asthma, atherosclerosis, thrombosis, platelet aggregation, restenosis, metastasis, influenza, incontinence, stroke, burn, trauma, acute pancreatitis, pyelonephritis, hepatitis, autoimmune disease, immunological disorder, senile dementia, insulin-dependent diabetes mellitus, disseminated intravascular coagulation, fatty embolism, Alzheimer's disease, adult or infantile respiratory disease, carcinogenesis or hemorrhage in a neonate) (all claimed).

ADVANTAGE - The compound have good bioavailability, posses potent analgesic and antiinflammatory properties and reduced potential for producing gastrointestinal lesions and does not have adverse side effects associated with prior art compounds.
Dwg.0/0

L33 ANSWER 13 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:368951 BIOSIS
DOCUMENT NUMBER: PREV200400365336
TITLE: New COX-2-selective CINODs.
AUTHOR(S): **Letts, L. Gordon**
SOURCE: Inflammopharmacology, (2003) Vol. 11, No. 4-6, pp.

515-516. print.
Meeting Info.: Inflammopharmacology 2003. Edinburgh, UK. April 22-24, 2003. Royal College of Physicians of Edinburgh.
ISSN: 0925-4692.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Sep 2004
Last Updated on STN: 8 Sep 2004

L33 ANSWER 14 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-691539 [74] WPIDS
DOC. NO. CPI: C2002-195387
TITLE: New substituted aryl compounds are cyclooxygenase-2 (COX-2) inhibitors, useful for e.g. treating, preventing or reducing inflammation, pain or fever.
DERWENT CLASS: B05
INVENTOR(S): EARL, R A; EZAWA, M; FANG, X; **GARVEY, D S**; GASTON, R D; KHANAPURE, S P
PATENT ASSIGNEE(S): (EARL-I) EARL R A; (EZAW-I) EZAWA M; (FANG-I) FANG X; (GARV-I) GARVEY D S; (GAST-I) GASTON R D; (KHAN-I) KHANAPURE S P; (NITR-N) NITROMED INC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002060378	A2	20020808	(200274)*	EN	132
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2002119977	A1	20020829	(200274)		
US 6706724	B2	20040316	(200420)		
EP 1406609	A2	20040414	(200426)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR					
AU 2002249812	A1	20020812	(200427)		
US 2004116431	A1	20040617	(200440)		
US 6825185	B2	20041130	(200479)		
JP 2005502587	W	20050127	(200510)		232
US 2005059665	A1	20050317	(200521)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002060378	A2	WO 2001-US48823	20011221
US 2002119977	A1 Provisional	US 2000-256932P	20001221
		US 2001-24046	20011221
US 6706724	B2 Provisional	US 2000-256932P	20001221
		US 2001-24046	20011221
EP 1406609	A2	EP 2001-998052	20011221
		WO 2001-US48823	20011221
AU 2002249812	A1	AU 2002-249812	20011221
US 2004116431	A1 Provisional	US 2000-256932P	20001221

Searcher : Shears 571-272-2528

		Div ex	US 2001-24046	20011221
			US 2003-730979	20031210
US 6825185	B2	Provisional	US 2000-256932P	20001221
		Div ex	US 2001-24046	20011221
			US 2003-730979	20031210
JP 2005502587	W		WO 2001-US48823	20011221
			JP 2002-560574	20011221
US 2005059665	A1	Provisional	US 2000-256932P	20001221
		Div ex	US 2001-24046	20011221
		Cont of	US 2003-730979	20031210
			US 2004-969079	20041021

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1406609	A2	Based on	WO 2002060378
AU 2002249812	A1	Based on	WO 2002060378
US 2004116431	A1	Div ex	US 6706724
US 6825185	B2	Div ex	US 6706724
JP 2005502587	W	Based on	WO 2002060378
US 2005059665	A1	Div ex	US 6706724
		Cont of	US 6825185

PRIORITY APPLN. INFO: US 2000-256932P 20001221; US 2001-24046 20011221; US 2003-730979 20031210; US 2004-969079 20041021

AN 2002-691539 [74] WPIDS

AB WO 200260378 A UPAB: 20021118

NOVELTY - Substituted aryl compounds (I) are new.

DETAILED DESCRIPTION - Substituted aryl compounds of formula (I) and their salts are new;

For Full Definitions see Definition Field.

INDEPENDENT CLAIMS are also included for:

(1) a method (M1) of improving the cardiovascular profile of a COX-2 selective inhibitor in a patient comprising administering (I);

(2) a composition (C1) comprising (I), at least one compound (Cp1) that donates, transfers or releases nitric oxides or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase and optionally at least one therapeutic agent;

(3) a kit comprising (I) or its salts.

ACTIVITY - Antiinflammatory; Analgesic; Antipyretic; Antiarthritic; Antiasthmatic; Gynecological; Tocolytic; Cytostatic; Ophthalmological; Antiallergic; Antibacterial; Immunosuppressive; Antiarteriosclerotic; Vulnerary; Antiulcer; Vasotropic; Antianginal; Cardiant; Anticoagulant; Thrombolytic; Hypotensive; Cerebroprotective.

MECHANISM OF ACTION - Cyclooxygenase-2 (COX-2) inhibitor.

The assay for COX-2 enzyme activity in the human whole blood was performed as described in Brideau et al; Inflamm Res; 45: 68-74 (1996). Human blood (at most 50 mL) not containing any aspirin and nonsteroidal anti-inflammatory compounds (NSAIDs) for 14 days was collected and placed in polypropylene syringes containing sodium heparin (20 units per mL blood, final concentration). The blood was distributed in aliquots per well of 24 well tissue culture plates. The plates were then placed on a gently rotating platform shaker in a 5% CO2 incubator at 37 deg. C for 15 minutes. 4-(1-(3',5'-Difluorophenyl)-1-oxomethyl)-1,2-methylenedioxy-5-(4-methylsulfonylphenyl)benzene (A)

was dissolved in dimethylsulfoxide (DMSO). The dilution of (A) (1 micro L) was added per well. To induce COX-2, lipopolysaccharide (LPS) from E. Coli was added at 10 micro g/mL to wells, 15 minutes after the addition of the (A). The resulting solution was transferred by polyethylene transfer pipettes to polypropylene centrifuge tube and centrifuged for 10 minutes at 4 deg. C. plasma (100 micro L) was removed from blood sample and added to methanol (1 mL) in new polypropylene centrifuge tubes, vortexed and stored overnight at -20 deg. C. The next day, the sample was centrifuged for 10 minutes at 4 deg. C and the supernatant was evaporated to dryness.

The sample was assayed for % inhibition for COX-2 enzyme activity and was found to be 100% of inhibition in human whole blood by (A).

USE - For treating, preventing or reducing inflammation, pain or fever; for treating or preventing a disorder resulting from elevated levels of COX-2 (e.g. angiogenisis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation and/or microbial infection, cardiovascular disorder, urinary and/or urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition and/or prevention of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition and/or prevention of platelet aggregation); for **treating** or **preventing** **gastrointestinal disorder** (e.g. an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia); for facilitating wound healing (e.g. ulcer); for treating or reversing renal or other toxicities (all claimed). Also for treating restenosis, atherogenesis, angina, ischemic disease, congestive heart failure or pulmonary edema associated with acute myocardial infarction, thrombosis, controlling blood pressure in hypertension, thromboemboembolic events, platelet aggregation, platelet adhesion, smooth muscle cell proliferation, vascular complications associated with the use of medical devices, wounds associated with the use of medical device, cerebrovascular ischemic events or stroke.

ADVANTAGE - At low dosages, the compound is a potent analgesic, has antiinflammatory and gastroprotective properties, has unexpected potential for facilitating wound healing, decreasing renal toxicity and dyspepsia and has improved cardiovascular profile of COX-2 inhibitor.

Dwg.0/0

L33 ANSWER 15 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER:	2002-225943 [28] WPIDS
CROSS REFERENCE:	2000-399322 [34]; 2002-048251 [06]; 2004-021519 [02]
DOC. NO. CPI:	C2002-068795
TITLE:	New nitrosated and/or nitrosylated nonsteroidal anti-inflammatory compounds used for treating e.g. inflammation, pain and fever.
DERWENT CLASS:	B05
INVENTOR(S):	BANDARAGE, U K; DONG, Q; FANG, X; **GARVEY, D S**

; MERCER, G J; RICHARDSON, S K; SCHROEDER, J D; WANG, T

PATENT ASSIGNEE(S): (BAND-I) BANDARAGE U K; (DONG-I) DONG Q; (FANG-I) FANG X; (GARV-I) GARVEY D S; (MERC-I) MERCER G J; (RICH-I) RICHARDSON S K; (SCHR-I) SCHROEDER J D; (WANG-I) WANG T; (NITR-N) NITROMED INC

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002016322	A1	20020207	(200228)*		65
US 6593347	B2	20030715	(200348)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002016322	A1 CIP of	US 1998-182433	19981030
	Div ex	US 1999-429019	19991029
		US 2001-938560	20010827
US 6593347	B2 CIP of	US 1998-182433	19981030
	Div ex	US 1999-429019	19991029
		US 2001-938560	20010827

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2002016322	A1 Div ex	US 6297260
US 6593347	B2 Div ex	US 6297260

PRIORITY APPLN. INFO: US 1999-429019 19991029; US 1998-182433 19981030; US 2001-938560 20010827

AN 2002-225943 [28] WPIDS

CR 2000-399322 [34]; 2002-048251 [06]; 2004-021519 [02]

AB US2002016322 A UPAB: 20040107

NOVELTY - Nitrosated and/or nitrosylated nonsteroidal antiinflammatory compounds (I)-(IV), are new.

DETAILED DESCRIPTION - Nitrosated and/or nitrosylated nonsteroidal antiinflammatory compounds of formulae (I)-(IV), are new.

Rg = H or lower alkyl;

Rh = 4-(thiophen-2-ylcarbonyl)phenyl, 3-benzoylphenyl, 4-(2,3-dihydro-isoindol-1-one)phenyl, 1,8-diethyl,1,3,4,9-tetrahydro-pyrano(3,4-b)indolyl, 1-methyl-2-(4-methylphenylcarbonyl)-pyrrol-5-yl, 3-fluoro-4-phenylphenyl, 1-(4-chlorophenylcarbonyl)-5-methoxy-2-methyl-indol-1-yl, 3-chloro-9H-carbazol-7-yl, 2-(phenylcarbonyl)-thiophen-5-yl, 3-phenoxyphenyl, , 2-methoxy-naphthalene-6-yl, 4-(imidazo(1,2-a)pyridine-2-yl)phenyl, 2,3-diphenyl-oxazol-5-ylmethyl, 4-(2-methylpropyl)phenyl, 2-(2,6-dichlorophenylamino)phenyl, 4-phenylphenyl-carbonylmethyl, 2-((2,6-dichlorophenyl)amino)phenylmethylcarbonyloxy, 4-allyloxy-3-chlorophenyl, 2-amino-3-benzoylphenyl, 2-(4-chlorophenyl)-benzoxazole-5-yl, 3-chloro-4-cyclohexylphenylcarbonylmethyl, 1-(3-phenylpropenoyl)-2-methyl-5-methoxyindol-3-yl, (1-(4-chlorophenylcarbonyl)-2-methyl-5-methoxy-indol-5-yl)methylcarbonyloxy, 4-(2-methylpropen-2-ylamino)phenyl, (1-benzyl-1H-indazol-3-yl)oxy, 2-amino-3-(4-bromophenylcarbonyl)phenyl, 1,3,4-triphenyl-1H-pyrazol-5-yl,

3-(4-chlorophenyl)-1-phenyl-pyrazol-4-yl, 10-methyl-10H-phenothiazine-2-yl, 3-chloro-4-(2,5-dihydropyrrol-1-yl)phenyl, 10H-9-oxa-1-aza-anthracen-6-yl, 4-phenylphenyl, 6,11-dihydrodibenz(b,e)oxepin-9-yl, 2-methyl-6,11-dihydrodibenzo(b,e)oxepin-9-yl, 4-(2-oxocyclopentylmethyl)phenyl, 3,4-bis-(4-methoxyphenyl)-isoxazol-5-yl, 4-(4-chlorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl, 2-(4-chlorophenyl)-thiazole-4-yl, 2-(4-fluorophenyl)-benzoxazole-5-yl, 7-methoxy-10-methyl-10H-phenothiazin-2-yl, 11H-dibenzo(b,f)thiepin-10-on-2-yl, 2-(4-chlorophenylcarbonyl)-1,3-dimethylpyrrol-5-yl, 4-(4-chlorophenyl)-2-phenyl-thiazole-5-yl, 2-aminocarbonylphenoxy, 2-benzoylthiophen-2-yl, 4-(3-hydroxyiminocyclohexyl)-phenyl, 1,2-diphenyl-4-butyl-3,5-dioxo pyrazolidin-4-yl-methyloxycarbonylmethyl, 4,5-diphenyloxazol-2-ylmethyl or a group of formula (i) or (ii);

n = 0 or 1;

X = -T-Bl-A-T-NOs;

A = -W-Bt-, -Ly-Bx, -W-Bt-Wx-Bk-, -(C(Rb)(Rc))p-Ex-, -G-Bt-Wz-Bk-Gx-Br, -J-Ex- or -C(Re)=N-Ez;

s = 1 or 2;

T = a covalent bond, carbonyl, O, S(O)o or -N(Ra)Ri;

o = 0-2;

Ra = a lone pair of electrons, H or alkyl;

Ri = e.g. H, alkyl, aryl, sulfonamido, carboxamido, carboxylic ester, amino alkyl, amino aryl, -CH2-C(T-Q)(Re)(Rf) or -(N2O2)-M+;

M+ = organic or inorganic cation;

L = CO, CS, T, heterocyclyl, aryl, alkenyl, alkynyl, arylheterocyclyl or (CH2CH2O)q;

q = 1-5;

B = alkyl, aryl, -(C(Re)(Rf))p, heterocyclyl, arylheterocyclyl or -(CH2CH2O)p;

p = 1-10;

Re, Rf = B1, H, alkyl or aryl, or

Re + Rf = a group Q1;

B1 = B2, -T-NOs or (C(Re)(Rf))k-T-NOs;

B2 = e.g. cycloalkoxy, halo, hydroxy, hydroxyalkyl, alkoxyalkyl, arylheterocyclic ring, alkylaryl, cycloalkylalkyl, heterocyclicalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, arylamino or diarylamino;

Q1 = heterocyclyl, or optionally bridged cycloalkyl;

Rb, Rc = haloalkyl, alkenyl, alkynyl, bridged cycloalkyl, heterocyclyl or B1, or

Rb + Rc = carbonyl, methanthial or Q1;

G = covalent bond, -T-C(O)-, -C(O)-T or T;

J = carbonyl, phosphoryl or silyl;

k, l, t, z, y = 1-3;

x, r = 0-3;

E = CO, CS, T, (C(Re)(Rf))p, alkyl, aryl, heterocyclyl, arylheterocyclyl or (CH2CH2O)q;

W = O, -S(O)o-, -N(Ra)Ri-, carbonyl or methanthial;

Rk = e.g. 2-(2,6-dichloro-3-methylphenylamino)-phenyl, 2-(2,3-dimethylphenylamino)-phenyl, 2-(methylcarbonyloxy)phenyl, 2-hydroxyphenyl, or 2',4'-difluoro-2-hydroxybiphenyl-3-yl,

Z = aryl;

A1-A3 = subunits of a 5- or 6-membered monocyclic aromatic ring selected from C-Ro, N-Rp, S, O, or Ba=Bb;

Ro = H, alkyl, alkoxyalkyl, halo, or nitro;

Rp = a covalent bond to an adjacent ring atom in order to render the ring aromatic, H, alkyl, arylalkyl, aryl or heteroaryl;

Ba, Bb = N or C-Ro, and

Rm = alkyl or aryl,
with a specified proviso.
'Full_definitions' are given in the 'Definitions' section.
INDEPENDENT CLAIMS are included for the following:
(1) a composition containing one compound (I)-(V) and at least one compound (C1) that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and
(2) a kit comprising the composition.
ACTIVITY - Antiinflammatory; Analgesic; Antipyretic; Antiulcer; Cytostatic; Vasotropic; Cardiant; Antirheumatic; Antiarthritic; Osteopathic; Hypotensive; Antipsoriatic; Immunosuppressive; Antiasthmatic; Antiarteriosclerotic; Anticoagulant; Thrombolytic; Virucide; Uropathic; Cerebroprotective; Vulnerary; Tranquilizer; Hepatotropic; Nootropic; Antidiabetic; Neuroprotective; Ophthalmological.
In a rat paw edema test as described in Winter et al, Proc. Society Exp. Biol. Med. 111: 544-547, 1962., 2-(4-methyl-4-(nitrosothio)piperidyl)ethyl 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate hydrochloride exhibited relative activity of 1.5 compared to diclofenac.
MECHANISM OF ACTION - Nitrosated and/or nitrosylated phosphodiesterase inhibitor.
USE - For treating, preventing or reducing inflammation, pain or fever; for treating or reversing the gastrointestinal, renal or other toxicities resulting from the use of a nonsteroidal antiinflammatory compound; for treating or preventing a gastrointestinal disorder in a patient including peptic ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a stress ulcer, a bleeding peptic ulcer, short bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; for treating an inflammatory disease or disorder including reperfusion injury to an ischemic organ, myocardial infarction, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, hypertension, psoriasis, organ transplant rejection, organ preservation, a female or male sexual dysfunction, radiation-induced injury, asthma, atherosclerosis, thrombosis, platelet aggregation, restenosis, metastasis, influenza, incontinence, stroke, burn, trauma, acute pancreatitis, pyelonephritis, hepatitis, an autoimmune disease, an immunological disorder, senile dementia, insulin-dependent diabetes mellitus, disseminated intravascular coagulation, fatty embolism, Alzheimer's disease, adult or infantile respiratory disease, carcinogenesis or a hemorrhage in a neonate, and for treating or preventing an ophthalmic disease or disorder e.g. glaucoma, inflammation of the eye or elevation of intraocular pressure.
ADVANTAGE - The compounds decrease or reverse the gastrointestinal, renal and other toxicities resulting form the use of nonsteroidal antiinflammatory drugs. The compounds have good bioavailability.
Dwg.0/0

L33 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2001:721438 CAPLUS
DOCUMENT NUMBER: 135:288343
TITLE: Preparation and activity of nitrosated and nitrosylated nonsteroidal antiinflammatory compounds

INVENTOR(S): Bandarage, Upul K.; Dong, Qing; Fang, Xinqin; **Garvey, David S.**; Mercer, Gregory J.; Richardson, Stewart K.; Schroeder, Joseph D.; Wang, Tiansheng

PATENT ASSIGNEE(S): Nitromed, Inc., USA

SOURCE: U.S., 59 pp., Cont.-in-part of U.S. Ser. No. 182,433, abandoned.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

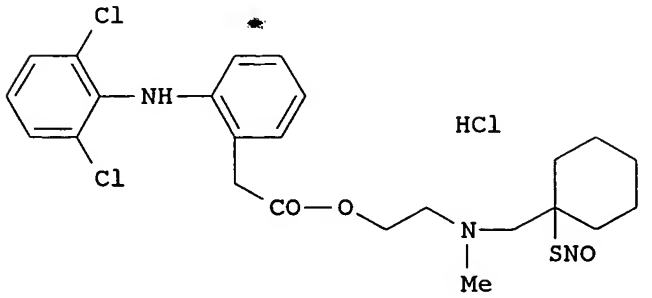
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6297260	B1	20011002	US 1999-429019	19991029
CA 2348741	AA	20000511	CA 1999-2348741	19991029
WO 2000025776	A1	20000511	WO 1999-US25481	19991029
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1126838	A1	20010829	EP 1999-958708	19991029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002528495	T2	20020903	JP 2000-579217	19991029
AU 763000	B2	20030710	AU 2000-16012	19991029
US 2002016322	A1	20020207	US 2001-938560	20010827
US 6593347	B2	20030715		
US 2003207919	A1	20031106	US 2003-431457	20030508

PRIORITY APPLN. INFO.:

US 1998-182433	B2	19981030
US 1999-429019	A3	19991029
WO 1999-US25481	W	19991029
US 2001-938560	A3	20010827

OTHER SOURCE(S): MARPAT 135:288343

GI



I

Searcher : Shears 571-272-2528

AB The present invention describes novel nitrosated and/or nitrosylated nonsteroidal antiinflammatory compds., and novel compns. comprising at least one nitrosated and/or nitrosylated nonsteroidal antiinflammatory compound, and, optionally, at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. The present invention also provides methods for treating, preventing and/or reducing inflammation, pain, and fever; decreasing or reversing the gastrointestinal, renal and other toxicities resulting from the use of nonsteroidal antiinflammatory drugs; **treating** and/or **preventing gastrointestinal disorders; treating** inflammatory **disease** states and disorders; and **treating** and/or preventing ophthalmic diseases or disorders. Thus, I was prepared in 8 steps from cyclohexanecarboxaldehyde and shows a relative activity of 1, 1.2 and 0.02 in analgesic, antiinflammatory and gastric lesion tests.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 17 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:55526 BIOSIS
DOCUMENT NUMBER: PREV200200055526
TITLE: Methods to treat gastrointestinal lesions and to reduce drug-induced gastrointestinal or renal toxicity.
AUTHOR(S): **Garvey, David S.** [Inventor]; **Letts, L. Gordon** [Inventor]; Renfroe, H. Burt [Inventor]; Tam, Sang William [Inventor]
CORPORATE SOURCE: ASSIGNEE: NitroMed, Inc.
PATENT INFORMATION: US 6323234 November 27, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 27, 2001) Vol. 1252, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jan 2002
Last Updated on STN: 25 Feb 2002

AB Nonsteroidal antiinflammatory drugs which have been substituted with a nitrogen monoxide group; composition comprising (i) a nonsteroidal antiinflammatory drug, which can optionally be substituted with a nitrogen monoxide group and (ii) a compound that directly donates, transfers or releases a nitrogen monoxide group (preferably as a charged species, particularly nitrosonium); and methods of treatment of inflammation, pain, gastrointestinal lesions and/or fever using the compositions are disclosed. The compounds and compositions protect against the gastrointestinal, renal and other toxicities that are otherwise induced by nonsteroidal antiinflammatory drugs.

L33 ANSWER 18 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2001-496643 [54] WPIDS
DOC. NO. CPI: C2001-149121
TITLE: New nitrosated and nitrosylated cyclooxygenase-2 inhibiting compounds used for **treating** inflammation, pain and **gastrointestinal**

disorders.

DERWENT CLASS: B05

INVENTOR(S): BANDARAGE, R R; BANDARAGE, U K; FANG, X; **GARVEY, D S; LETTS, L G;** SHROEDER, J D; TAM, S W; SCHROEDER, J D

PATENT ASSIGNEE(S): (NITR-N) NITROMED INC; (BAND-I) BANDARAGE R R; (BAND-I) BANDARAGE U K; (FANG-I) FANG X; (GARV-I) GARVEY D S; (LETT-I) LETTS L G; (SCHR-I) SCHROEDER J D; (TAMS-I) TAM S W

COUNTRY COUNT: 95

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001045703	A1	20010628	(200154)*	EN	227
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001025928	A	20010703	(200164)		
US 2001041726	A1	20011115	(200172)		
EP 1246621	A1	20021009	(200267)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
KR 2002067574	A	20020822	(200310)		
BR 2000017037	A	20030610	(200341)		
JP 2003523958	W	20030812	(200355)		272
CN 1434712	A	20030806	(200366)		
US 6649629	B2	20031118	(200376)		
US 2003220228	A1	20031127	(200378)		
ZA 2002005707	A	20040128	(200420)		251
NZ 519781	A	20040430	(200431)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001045703	A1		WO 2000-US35014	20001222
AU 2001025928	A		AU 2001-25928	20001222
US 2001041726	A1	Provisional	US 1999-171623P	19991223
		Provisional	US 2000-226085P	20000818
			US 2000-741816	20001222
EP 1246621	A1		EP 2000-989422	20001222
			WO 2000-US35014	20001222
KR 2002067574	A		KR 2002-708246	20020624
BR 2000017037	A		BR 2000-17037	20001222
			WO 2000-US35014	20001222
JP 2003523958	W		WO 2000-US35014	20001222
			JP 2001-546642	20001222
CN 1434712	A		CN 2000-819154	20001222
US 6649629	B2	Provisional	US 1999-171623P	19991223
		Provisional	US 2000-226085P	20000818
			US 2000-741816	20001222
US 2003220228	A1	Provisional	US 1999-171623P	19991223
		Provisional	US 2000-226085P	20000818
		Div ex	US 2000-741816	20001222
			US 2003-463671	20030618

Searcher : Shears 571-272-2528

ZA 2002005707	A	ZA 2002-5707	20020717
NZ 519781	A	NZ 2000-519781	20001222
		WO 2000-US35014	20001222

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001025928	A	Based on	WO 2001045703
EP 1246621	A1	Based on	WO 2001045703
BR 2000017037	A	Based on	WO 2001045703
JP 2003523958	W	Based on	WO 2001045703
NZ 519781	A	Div in	NZ 530757
		Based on	WO 2001045703

PRIORITY APPLN. INFO: US 2000-226085P 20000818; US 1999-171623P 19991223; US 2000-741816 20001222; US 2003-463671 20030618

AN 2001-496643 [54] WPIDS

AB WO 200145703 A UPAB: 20020321

NOVELTY - Sixteen nitrosated and nitrosylated cyclooxygenase-2 inhibiting compounds are new.

DETAILED DESCRIPTION - Sixteen nitrosated and nitrosylated cyclooxygenase-2 inhibiting compounds e.g. compounds of formula (I)-(VII) are new.

X4, Z4 = N or CR21;

R20 = SO2-Me, SO2-NR8(D1) or SO2-N(D1)-CO-CF3;

R21, R21' = H, lower alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, CN, CO2D1, CO2R14, lower alkyl-O-D1, lower alkyl-CO2D1, lower alkyl-CO2R14, halo, O-D1, N3, NO2, NR14D1, N(D1)COR14, NHK, aryl, arylalkylthio, arylalkoxy, alkylamino, aryloxy, alkylarylalkylamino, cycloalkylalkylamino or cycloalkylalkoxy;

R22 = phenyl, pyridinyl or its N-oxide (all optionally substituted by 1-3 halo, alkoxy, alkylthio, CN, lower alkyl, haloalkyl, N3, CO2D1, CO2-lower alkyl, C(R14)(R15)-OD1, OD1, lower alkyl-CO2-R14 or lower alkyl-CO2-D1), T-C(R23)(R24)-(C(R25)(R26))o-C(R27)(R28)-U-D1, arylalkyl, cycloalkylalkyl or a group of formula (i);

R14, R15 = H or lower alkyl;

R23-R28 = H or lower alkyl, or

CR23 + CR27, or CR27R28 = 3-7C carbocyclyl, or

R23 + R25 = a covalent bond;

Y5 = CR29R30, O or S;

R29, R30 = H, lower alkyl, (CH2)o-OD1 or halo, or

R29 + R30 = oxo;

s = 2-4;

R8 = H, K or R9;

R9 = lower alkyl, lower alkyl-CO2D1, lower alkyl-NHD1, cycloalkyl, K or phenyl, benzyl or benzoyl (all optionally substituted by 1-3 halo, lower alkyl, alkoxy, alkylthio, lower alkyl-CO2-D1, lower alkyl-ND1, CN, CO2D1 or haloalkyl);

D1 = H, V or K;

V = NO, NO2 or H;

K = Waa-Eb-(C(Re)(Rf))p-Ec-C(Re)(Rf)x-Wd-(C(Re)(Rf))y-Wi-Ej-Wg-(C(Re)(Rf))z-U-V;

aa, b, c, d, g, i, j = 0-3;

p, x, y, z = 0-10;

W = CO, CS, T, (C(Re)(Rf))h, alkyl, aryl, heterocyclyl,

arylheterocyclyl or (CH2CH2O)q;
E = T, alkyl, aryl, (C(Re)(Rf))h, heterocyclyl or (CH2CH2O)q;
h = 1-10;
q = 1-5;
Re, Rf = e.g. H, alkyl, cycloalkoxy, halo, OH, hydroxyalkyl, alkoxyalkyl or arylheterocyclyl, etc. or
Re + Rf = oxo or thial, or
CReRf = heterocyclyl, cycloalkyl (optionally bridged);
T = a covalent bond, carbonyl, O, S(O)o or N(Ra)Ri;
o = 0-2;
Ra = electron lone pair, H or lower alkyl;
Ri = e.g. H, alkyl, aryl or alkylcarboxylic acid, etc.
U = O, S or N(Ra)Ri;
X5 = O or S, or
C(=X5)U = 5-7 membered heterocyclyl;
R31 = alkoxy, haloalkoxy, alkylthio, haloalkyl, halo or lower alkyl;
R32-R37 = H, halo, lower alkyl, cycloalkyl, haloalkyl, OD1, OR43, SD1, SR43, S(O)R43, S(O)2R43 or phenyl or benzyl (both optionally substituted by haloalkyl, CN, halo, lower alkyl, OR43, SR43, S(O)R43 or S(O)2R41), or
R32 + R33, R34 + R35, or R36 + R37 = oxo, or
CR32R33, or CR34R35, CR36R37 = saturated 3-7 membered monocyclic ring optionally containing one heteroatom, or
CR33R34, CR33CR36 or CR34R36 = saturated or aromatic 3-7 membered monocyclic ring;
R38, R39 = H, or
R38 + R39 = oxo;
R40-R42 = H, halo, lower alkyl, alkoxy, alkylthio, S(O)-lower alkyl, haloalkyl, CN, N3, NO2SCF3, or OCF3;
R43 = lower alkyl or benzyl (optionally substituted by haloalkyl, CN, halo or lower alkyl);
n = 0 or 1;
X8 = O, S, NRi or CR58R59;
A1-A4 = C or N, provided that at least 2 of A1-A4 are C;
R54 = haloalkylalkyl, halo, alkylthio, alkoxy, NO2, CN, lower alkyl-CN, heterocyclyl, lower alkyl, arylalkyl, cycloalkyl, or phenyl (optionally substituted by 1 or 2 alkylthio, NO2 or alkylsulfonyl;
R55 = CO2D1, CO-N(R8)2, CO2-lower alkyl, CO-N(D1)-SO2-(C(Re)(Rf))p-U-V or CO2-lower alkyl-UV;
R56 = H, phenyl, thienyl, alkynyl, alkenyl or alkyl;
Rg = e.g. H, lower alkyl, arylalkyl or alkoxy, etc. or
Rg + the ring including A1-A4 = naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl or dibenzofuryl;
R58, R59 = H, lower alkyl, lower alkylphenyl, haloalkyl, halo, NO2, CN, lower alkyl-CN, alkoxy, alkylthio or alkenyl, or
CR58R59 = cycloalkyl;
X11 = O or CH2;
Y11 = O, H2, N-OD, N-O-lower alkyl, N-O-aryl, N-COO-lower alkyl, N-N(R8)2 or N-N(R8)-SO2-lower alkyl;
R62-R65 = H, lower alkyl, alkoxy, halo, CN, OD1, aryloxy, NR12R13, CF3, NO2, alkylthio, S(O)o-lower alkyl, C(O)N(R8)2, CO2D1, CO2-lower alkyl or NR8-CO-lower alkyl;
R66 = H, lower alkyl, alkenyl, alkoxyalkyl or cycloalkylalkyl;
R12, R13 = H, lower alkyl or aryl;
X13, Y13 = =C(H)- or =N-;
R90 = lower alkyl, lower alkyl-OD1, alkenyl, lower alkyl-CN, lower alkyl-CO2D1, aryl, heterocyclyl or heterocyclylalkyl;
R91 = phenyl, 5 membered heteroaryl containing one S, O or N atom

and optionally 1-3 additional N atoms, or 6 membered heteroaryl containing one N atom and optionally 1-4 additional N atoms (all optionally substituted by halo, alkoxy, alkylthio, CN, haloalkyl, lower alkyl, CO2D1, CO2-lower alkyl, CO2D1, CO2-lower alkyl, lower alkyl-OD1, lower alkyl-NR12R13, lower alkyl-CO2D1 or OD1;

provided that (I)-(V) contain at least one nitrite, nitrate, thionitrite or thionitrate group.

See 'Definitions' for 'Full definitions'.

An INDEPENDENT CLAIM is included for a composition comprising at least one of the 16 compounds as above and at least one compound that donates, transfers or releases nitric oxide, or induces production of endogenous nitric oxide or endothelium derived relaxing factor, or is a substrate for nitric oxide synthase.

ACTIVITY - Antiinflammatory; analgesic; antipyretic; gastrointestinal; antiulcer, vulnerary; antiarthritic; antiasthmatic; respiratory; dermatological; antiarteriosclerotic; cytostatic; ophthalmological; antiallergic; antibacterial; immunosuppressive; cardiant; uropathic; CNS.

MECHANISM OF ACTION - Cyclooxygenase-2 (COX-2) inhibitor.

In an assay for human COX-1 and COX-2 activity using the COX Inhibitor Screening Assay (Cayman Chemical, Ann Arbor, MI, which also contained the Prostaglandin Screening EIA Kit, used for prostaglandin quantification), 4-(5-((nitrooxy)methyl)-3-phenylisoxazol-4-yl)benzenesulfonamide at 10 mu M exhibited an IC50 value of 100% for COX-2 inhibition compared to 0 for COX-1 inhibition.

USE - Used for treating inflammation, pain, fever, gastrointestinal disorders (e.g. inflammatory bowel disease, Crohn's diseases, gastritis, irritable bowel syndrome, ulcerative colitis, ulcers and Zollinger-Ellison syndrome), wounds, renal or other toxicities, angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, bursitis, skin related conditions, neoplasia, CNS disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, microbial infection, cardiovascular disorders, urinary and/or urological disorders, endothelial dysfunction, activation, adhesion and infiltration of neutrophils at the site of inflammation and platelet aggregation. The compounds are also used for preserving organs and tissues.

ADVANTAGE - The compounds are selective COX-2 inhibitors.

Dwg.0/5

L33 ANSWER 19 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:187929 BIOSIS
DOCUMENT NUMBER: PREV200200187929
TITLE: Enhanced gastroprotective and anti-ulcerogenic activities in rats of a new class of proton pump inhibitor containing nitrosothiol nitric oxide donor.
AUTHOR(S): Saha, Joy K. [Reprint author]; Wang, Tiansheng [Reprint author]; Stewart, Richardson [Reprint author]; Trocha, Mark [Reprint author]; Shumway, Mathew [Reprint author]; **Garvey, David** [Reprint author]; **Letts, L. Gordon** [Reprint author]; Wolfe, M. Michael; Tam, S. William
CORPORATE SOURCE: NitroMed, Inc, Bedford, MA, USA
SOURCE: Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.144-A.145. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. Atlanta, Georgia, USA. May 20-23, 2001. American

Gastroenterological Association; American Association for the Study of Liver Diseases; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002

L33 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2000:608578 CAPLUS
DOCUMENT NUMBER: 133:203023
TITLE: Nitrosated and nitrosylated proton pump inhibitors, compositions and methods of use
INVENTOR(S): **Garvey, David S.; Letts, L. Gordon;** Tam, Sang William; Wang, Tiansheng; Richardson, Stewart K.
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050037	A1	20000831	WO 2000-US2524	20000225
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2362930	AA	20000831	CA 2000-2362930	20000225
EP 1154771	A1	20011121	EP 2000-910039	20000225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537336	T2	20021105	JP 2000-600648	20000225
US 6852739	B1	20050208	US 2000-512829	20000225
US 2004266828	A1	20041230	US 2004-866303	20040614

PRIORITY APPLN. INFO.: US 1999-122111P P 19990226
US 2000-512829 A3 20000225
WO 2000-US2524 W 20000225

OTHER SOURCE(S): MARPAT 133:203023
AB The invention describes nitrosated and/or nitrosylated proton pump inhibitor compds., as well as compns. comprising ≥1 proton pump inhibitor compound that is optionally substituted with ≥1 NO and/or NO2 group, and, optionally, ≥1 compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived

relaxing factor, or is a substrate for nitric oxide synthase, and/or ≥1 nonsteroidal antiinflammatory drug, selective COX-2 inhibitor antacid, bismuth-containing reagent, acid-degradable antibacterial compound, and mixts. thereof. The invention also provides methods for **treating** and/or **preventing** **gastrointestinal disorders**; facilitating ulcer healing; decreasing the recurrence of ulcers; improving gastroprotective properties, anti-Helicobacter pylori properties or antacid properties of proton pump inhibitors; decreasing or reducing the gastrointestinal toxicity associated with the use of nonsteroidal antiinflammatory compds.; and treating Helicobacter pylori and viral infections. The compds. and/or compns. of the present invention can also be provided in the form of a pharmaceutical kit. Preparation of e.g. nitrosylated lansoprazole is described. Compared to lansoprazole, the nitrosylated lansoprazole significantly inhibited the formation of EtOH/HCl-induced gastric lesions.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2000:351366 CAPLUS
DOCUMENT NUMBER: 133:4658
TITLE: Preparation of nitrosated and nitrosylated H2 receptor antagonists as drugs.
INVENTOR(S): **Garvey, David S.; Letts, L. Gordon**; Wang, Tiansheng
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

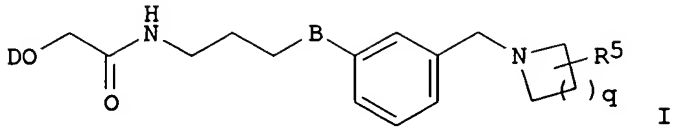
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000028988	A1	20000525	WO 1999-US27207	19991117
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2349575	AA	20000525	CA 1999-2349575	19991117
EP 1140066	A1	20011010	EP 1999-962784	19991117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002077343	A1	20020620	US 1999-441891	19991117
US 6552047	B2	20030422		
JP 2002529503	T2	20020910	JP 2000-582035	19991117
AU 772188	B2	20040408	AU 2000-19152	19991117
US 2003060492	A1	20030327	US 2002-282071	20021029
PRIORITY APPLN. INFO.:			US 1998-108877P P	19981117
			US 1999-140839P P	19990628

US 1999-441891 A3 19991117

WO 1999-US27207 W 19991117

OTHER SOURCE(S): MARPAT 133:4658

GI



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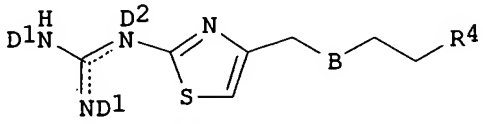

II

AB R1D1NC(:AR2)ND1CH2CH2BCH2R3, (I, II; A = CH, N, S; B = O, S, SO, SO2, CH2; D1 = H, NO, NO2, etc.; R1 = H, alkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl; R2 = electron lone pair, cyano, NO2, alkylsulfonyl, arylsulfonyl, alkylcarbonyl, carboxamido, carboxylic ester, cycloalkylalkyl; R3 = specified imidazolyl, aminomethylthiazolyl, aminomethylfuryl groups; R5 = H, OH, hydroxyalkyl; D2 = D1, electron lone pair; R4 = C(:ND1)ND1SO2NHD1, etc.; q = 1-5; with provisos), were prepared Thus, a cooled solution of 2-[2-(nitrosothio)adamantan-2-yl]acetic acid (preparation given) and (2Z)-2-aza-3-methylamino-3-[[2-[(5-methylimidazol-4-yl)methylthio]ethyl]amino]prop-2-enenitrile in CH2Cl2 were treated with DCC followed by warming to room temperature and stirring for 1 h to give 26.5% (2Z)-2-aza-3-methylamino-3-[[2-[[5-methyl-1-[2-[2-(nitrosothio)adamantan-2-yl]acetyl]imidazol-4-yl]methylthio]ethyl]amino]prop-2-enenitrile. This at 160 μmol/kg orally significantly inhibited ethanolic HCl-induced gastric lesions in rats.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 22 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-399322 [34] WPIDS

CROSS REFERENCE: 2002-048251 [06]; 2002-225943 [28]; 2004-021519 [02]

DOC. NO. CPI: C2000-120493

TITLE: New nitrosated or nitrosylated derivatives of non-steroidal antiinflammatory drugs, used for **treatment** of inflammatory, **gastrointestinal** or ophthalmological **diseases.**

DERWENT CLASS: B05

INVENTOR(S): BANDARAGE, U K; DONG, Q; FANG, X; **GARVEY, D S**; MERCER, G J; RICHARDSON, S K; SCHROEDER, J D; WANG, T

PATENT ASSIGNEE(S): (NITR-N) NITROMED INC

COUNTRY COUNT: 91

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000025776	A1	20000511	(200034)*	EN	157
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 2000016012	A	20000522	(200040)		
EP 1126838	A1	20010829	(200150)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2002528495	W	20020903	(200273)		224
AU 763000	B	20030710	(200355)		
AU 2004200091	A1	20040205	(200443)#		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000025776	A1	WO 1999-US25481	19991029
AU 2000016012	A	AU 2000-16012	19991029
EP 1126838	A1	EP 1999-958708	19991029
		WO 1999-US25481	19991029
JP 2002528495	W	WO 1999-US25481	19991029
		JP 2000-579217	19991029
AU 763000	B	AU 2000-16012	19991029
AU 2004200091	A1	AU 2004-200091	20040109

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000016012	A	Based on	WO 2000025776
EP 1126838	A1	Based on	WO 2000025776
JP 2002528495	W	Based on	WO 2000025776
AU 763000	B	Previous Publ.	AU 2000016012
		Based on	WO 2000025776
AU 2004200091	A1	Div ex	AU 763000

PRIORITY APPLN. INFO: US 1998-182433 19981030; AU 2004-200091 20040109

AN 2000-399322 [34] WPIDS

CR 2002-048251 [06]; 2002-225943 [28]; 2004-021519 [02]

AB WO 200025776 A UPAB: 20040709

NOVELTY - New nitrosated or nitrosylated derivatives of non-steroidal antiinflammatory compounds with improved bioavailability.

DETAILED DESCRIPTION - Aldehyde or ketone compounds of formula (I) or (II), fused pyrrolidinone derivatives of formula (III) or fused thiazine derivatives of formula (IV) are new.

Rg = H or lower alkyl;

Rh = one of 52 specific groups e.g. of formula (1)-(3);

X = -T-Bl-W-Bt-T-NOs or one of 6 other groups containing the -T-NOs terminal group;;

s = 1 or 2;

T = a bond, carbonyl, O, S(O)o etc.;

o = 0-2;

Ri = H, alkyl, aryl, alkyl- or aryl- carboxylic acids or their esters, alkyl- or aryl-carboxamido, alkylaryl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, sulfonamido, carboxamido, carboxylic ester, aminoalkyl, aminoaryl etc.;

Rk = 2-hydroxyphenyl, 2,5-dihydroxyphenyl, 2-hydroxy-5-amino-phenyl or one of 16 other specific groups;

Z' = aryl;

A1-A3 = CRo, S, O etc.;

W = O, S(O)o, carbonyl or methanthial etc.;

B = alkyl, aryl, heterocyclyl, heteroaryl or (CH2CH2 etc.;

Rm = alkyl or aryl;

l, t = 1-3.

provided that the compounds contain and NO or NO2 group.

ACTIVITY - Antiinflammatory; ophthalmological; antipyretic; analgesic; antiulcer; cytostatic; vasotropic; cardiant; antirheumatic; antiarthritic; osteopathic; hypotensive; antipsoriatic; immunosuppressant; antiasthmatic; antiarteriosclerotic; thrombolytic; anticoagulant; virucide; uropathic; cerebroprotective; vulnerary; hepatotropic; nootropic; neuroprotective; antidiabetic. In a phenylbenzoquinone-induced writhing test, 2-(4-methyl-4-(nitrosothio)piperidyl)ethyl-2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate hydrochloride had a relative activity of 1.5 (c.f. 1 for diclofenac (no dosage given).

MECHANISM OF ACTION - None given.

USE - (I) are useful for preventing or reducing inflammation, pain and fever, reversing the gastrointestinal, renal or other toxicity resulting from non-steroidal antiinflammatory drug (NSAID), **treating gastrointestinal disorders** (especially dyspepsia, peptic ulcer, **gastric** hyperacidity, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, stress ulcer, bleeding peptic ulcer, short bowel syndrome or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia), inflammatory disorders (especially reperfusion injury to an ischemic organ, myocardial infarction, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, hypertension, psoriasis, organ transplant rejection, organ preservation (sic), male or female sexual dysfunction, radiation induced injury, asthma, atherosclerosis, thrombosis, platelet aggregation, restenosis, metastasis, influenza, incontinence, stroke, burns, trauma, acute pancreatitis, pyelonephritis, hepatitis, autoimmune disease, immunological disorder, senile dementia, insulin-dependant diabetes mellitus, disseminated intravascular coagulation, fatty embolism, Alzheimer's disease, adult or infantile respiratory disease, carcinogenesis or hemorrhage in a neonate), ophthalmic disease (especially glaucoma, inflammation or raised intraoccular pressure) (all claimed).

ADVANTAGE - The compounds have improved bioavailability, have good activity and do not cause gastrointestinal ulcers

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L33 ANSWER 23 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1994-271856 [33] WPIDS

CROSS REFERENCE: 1991-008877 [02]

DOC. NO. CPI: C1994-124378

TITLE: Acylated peptide selective Type B CCK receptor agonists - used in **treating** CNS **disorders**, drug, alcohol, or nicotine abuse, **gastrointestinal** and endocrine disorders, shock etc..

DERWENT CLASS: B04
INVENTOR(S): BRODIE, M S; CHUNG, J Y; **GARVEY, D S**; HOLLADAY, M W; MAY, P D; NADZAN, A M; SHIOSAKI, K; SHUE, Y; TUFANO, M D
PATENT ASSIGNEE(S): (ABBO) ABBOTT LAB
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5340802	A	19940823	(199433)*		2

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5340802	A	CIP of	US 1989-375107	19890630
		CIP of	US 1990-531771	19900606
		CIP of	US 1991-791805	19911113
			US 1993-11055	19930129

PRIORITY APPLN. INFO: US 1989-375107 19890630; US 1990-531771 19900606; US 1991-791805 19911113; US 1993-11055 19930129

AN 1994-271856 [33] WPIDS
CR 1991-008877 [02]
AB US 5340802 A UPAB: 19941010

Peptides acylated at the N-terminal, of formula A-B-Y-Z (I), and their salts are new. In the formula A = an acyl gp. (a) or (b); R1 = H, halo, OH, 1-6 alkoxy or alkylthio, amino, mono- and di(1-6C alkyl)amino, N-protected amino, N-protected 1-6C alkylamino or R5-R4-CONR3-; R2 = naphthyl, phenyl or benzoHet, each opt. mono-substd.; R3 = H or 1-6C alkyl; R4 = 1-6C alkylene or 2-6C alkenylene; R5 = phenyl (opt. substd.); R6 = H, OH, halo, 1-6C alkyl, amino or mono- or di-(1-6C alkyl)amino; R7 = H, 1-6C alkyl, or 1-6C alkanoyl; B = an aminoacyl gp. (c) or (d); R8 = 1-6C alkyl, 1-6C alkoxy, 1-4C alkyl or 1-6C alkylthio, 1-4C alkyl; R9 = 2-4C alkylene; R10 = O, S, or is absent; R11 = H, 1-6C alkyl or alkoxy, 1-6C alkoxy, 1-4C alkyl or 1-6C alkylthio, 1-4C alkyl; Y = an aminoacyl gp. (e); R12 = COOH or tetrazolyl; Z = an aminoamide gp. (f), (g) or (h); R13 = 1-6C alkyl, 3-8C cycloalkyl, or Het, phenyl, naphthyl or benzoHet (all opt. monosubstd. by 1-6C alkyl, haloalkyl, alkoxy or alkylthio, halo, OH, 1-6C alkanoyl, COOH, amino, mono- and di-(1-6C alkyl)-amino, nitro oe OSO3H); Het = a 5-membered ring with 0-2 double bonds or 6-membered with 0-3 containing 1 or 2N, 1S or 1O, 1N and 1S, or 1N and 1O, opt. with the N quaternised; R14 = NHR15; R15 = H, OH, CH3 or NH2; provided that when R1 = amino, N-protected amino, or R5-R4-CONR3, then B = gp. (d) or Z = gp. (g) or (h). R16 = H, 1-6C alkyl, halo, 1-6C haloalkyl, 1-6C alkoxy, 1-6C alkylthio, OH, 1-6C alkoxycarbonyl, COOH, NH2, mono- or di(1-6C alkyl)amino, NO2 or OSO3H.

USE - (I) have cholecystokinin (CCK) type B receptor selective affinity agonists with applications in treatment and prevention of CCK-related disorders of the CNS endocrine and GI systems. They are useful in treatment of substance abuse, including drugs or alcohol or nicotine addiction; eating disorders and appetite control; disorders of memory and recognition in haemorrhagic shock, respiratory and cardiocirculatory insufficiencies; schizophrenia, convulsions,

neurodegeneration and Parkinson's disease.

L33 ANSWER 24 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1991-008877 [02] WPIDS
CROSS REFERENCE: 1994-271856 [33]
DOC. NO. CPI: C1991-003894
TITLE: New tetra peptide type-B cholecystokinin ligands - for **treatment** of CNS, **gastrointestinal**, endocrine and eating **disorders** also for shock, respiratory problems, etc..
DERWENT CLASS: B04
INVENTOR(S): BRODIE, M S; CHUNG, J Y L; **GARVEY, D S**; MAY, P D; NADZAN, A M; SHIOSAKI, K; SHUE, Y K; TUFANO, M D
PATENT ASSIGNEE(S): (ABBO) ABBOTT LAB; (SHIO-I) SHIOSAKI K
COUNTRY COUNT: 16
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 405506	A	19910102	(199102)*		
R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
PT 94562	A	19910208	(199109)		
CA 2020065	A	19901231	(199112)		
JP 03068597	A	19910325	(199118)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 405506	A	EP 1990-112261	19900627
JP 03068597	A	JP 1990-174287	19900630

PRIORITY APPLN. INFO: US 1989-375107 19890630; US 1990-531771 19900606
AN 1991-008877 [02] WPIDS
CR 1994-271856 [33]
AB EP 405506 A UPAB: 19941013
Peptides of formula A-B-C-D (I) are new. A = functionalised acetyl or R9-CO- where R9 = hetero or carbotricyclic. Specifically claimed A = BOC-Trp or Ctp; B = functionalised 2-aminopropionyl; or A-B together form functionalised piperazinedionyl or functionalised 5-amino-3-aza-4-keto-hexanoyl; Specifically claimed B = Met, Leu, Nle, Tpp or 1,4-thiazine-3-carbonyl. C = -N(R2O)-CH(CH2R21)-CO- D = functionalised ethylamino, functionalised tetrahydroisoquinolyl, functionalised piperazinol-1-yl, dehydro-Phe amide or an analogue of dehydro-Phe; Specifically claimed D = Phe-NH2, Tiq-NH2, dehydro Phe-NH2, (NMe)Phe-NH2, alpha-Nal-NH2 or beta-Nal-NH2; Tiq = (II); Ctp = (III); Tpp = (IV). Cpds. are specifically claimed e.g. Ctp-Leu-Asp-Phe-NH2 or BOC-Trp-Leu-Asp-Tiq-NH2. Preparation of (I) is also claimed.

USE/ADVANTAGE - For mimicking effects of CCK on type-B receptors for treating CNS disorders, enhancing learning, memory or appetite. Also for treating alcohol or nicotine addiction (claimed). Also for **gastrointestinal** and endocrine **disorders** and for **treatment** of shock, respiratory and cardiocirculatory insufficiencies. @(101pp Dwg.No.0/0)@

0/0

FILE 'HOME' ENTERED AT 12:48:16 ON 15 APR 2005

Searcher : Shears 571-272-2528

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=> d his ful

     (FILE 'REGISTRY' ENTERED AT 12:04:26 ON 15 APR 2005)
                DEL HIS Y
                ACT AUDET760A/A
               ---------
L1               STR
L2  (       115)SEA SSS FUL L1
L3               STR
L4           21 SEA SUB=L2 SSS FUL L3
               ---------
                D L3
                D QUE STAT

     FILE 'CAPLUS' ENTERED AT 12:20:21 ON 15 APR 2005
L5           37 SEA ABB=ON  PLU=ON  L4
                D L5 1-37 IBIB ABS HITSTR

     FILE 'CAOLD' ENTERED AT 12:21:30 ON 15 APR 2005
L6            0 SEA ABB=ON  PLU=ON  L4

     FILE 'USPATFULL' ENTERED AT 12:21:36 ON 15 APR 2005
L7            7 SEA ABB=ON  PLU=ON  L4
                D 1-7 IBIB ABS

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 12:22:01 ON 15 APR 2005
L8           43 SEA ABB=ON  PLU=ON  L4
L*** DEL     36 DUP REM L8 (7 DUPLICATES REMOVED)
                D KWIC
L9            0 SEA ABB=ON  PLU=ON  L8 AND (PEPTIC OR UCLER? OR GASTROINTES
                TIN? OR GASTR? INTESTIN? OR (INTESTIN? OR GASTR## OR
                STOMACH)(S)(DISORDER OR DISEAS?))
L*** DEL      0 S L8 AND "GARVEY"?/AU
L*** DEL     36 DUP REM L8 (7 DUPLICATES REMOVED)
                D 1-43 IBIB ABS
L10          25 SEA ABB=ON  PLU=ON  L8 AND (TREAT? OR THERAP? OR PREVENT?)

L11          20 DUP REM L10 (5 DUPLICATES REMOVED)
                D 1-20 IBIB ABS

     FILE 'MARPAT' ENTERED AT 12:27:38 ON 15 APR 2005
                D L3
L12             STR L3
L13           0 SEA SSS SAM L12 (MODIFIED ATTRIBUTES)
L14           2 SEA SSS FUL L12 (MODIFIED ATTRIBUTES)
                D QUE STAT
                D 1-2 .BEVMAR1

     FILE 'MARPATPREV' ENTERED AT 12:28:38 ON 15 APR 2005
L15           0 SEA SSS FUL L12 (MODIFIED ATTRIBUTES)
                D QUE STAT

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
     JICST-EPLUS, JAPIO' ENTERED AT 12:29:11 ON 15 APR 2005
L16         663 SEA ABB=ON  PLU=ON  "GARVEY D"?/AU
L17         588 SEA ABB=ON  PLU=ON  ("LETTS L"? OR "LETTS G"?)/AU
L18         141 SEA ABB=ON  PLU=ON  L16 AND L17
L19         107 SEA ABB=ON  PLU=ON  (L16 OR L17 OR L18) AND (PEPTIC OR
                UCLER? OR GASTROINTESTIN? OR GASTR? INTESTIN? OR (INTESTIN?
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                OR GASTR## OR STOMACH)(S)(DISORDER OR DISEAS?))
L20          83 SEA ABB=ON  PLU=ON  L19 AND (TREAT? OR THERAP? OR PREVENT?)

L21          53 SEA ABB=ON  PLU=ON  (L16 OR L17 OR L18) AND (TREAT? OR
                THERAP? OR PREVENT?)(S)((PEPTIC OR GASTRODUODEN? OR GASTR?
                DUODEN? OR MARGINAL)(S) UCLER? OR (GASTROINTESTIN? OR
                GASTR? INTESTIN? OR INTESTIN? OR GASTR## OR STOMACH)(S)(DIS
                ORDER OR DISEAS?))

     FILE 'REGISTRY' ENTERED AT 12:37:32 ON 15 APR 2005

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
     JICST-EPLUS, JAPIO' ENTERED AT 12:37:38 ON 15 APR 2005
L22          39 DUP REM L21 (14 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 12:37:58 ON 15 APR 2005
                E "N-(3-NITRATOPIVALOYL)-S-PIVALOYL-CYSTEINE ETHYL ESTER"/C

     FILE 'CAPLUS' ENTERED AT 12:38:44 ON 15 APR 2005
L23           4 SEA ABB=ON  PLU=ON  (3(W)(NITRATOPIVALOYL OR NITRATOPIVALOY
                L))(S)CYSTEIN#
                D KWIC
L24           4 SEA ABB=ON  PLU=ON  L23(S)ESTER
L25           0 SEA ABB=ON  PLU=ON  L24 NOT L5

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
     JICST-EPLUS, JAPIO' ENTERED AT 12:39:51 ON 15 APR 2005
L26          37 SEA ABB=ON  PLU=ON  L24
L27           4 SEA ABB=ON  PLU=ON  L26 AND (PEPTIC OR UCLER? OR GASTROINTE
                STIN? OR GASTR? INTESTIN? OR (INTESTIN? OR GASTR## OR
                STOMACH)(S)(DISORDER OR DISEAS?))
                D KWIC
                D KWIC 2-3
L28           0 SEA ABB=ON  PLU=ON  L26(S)("S" PIVALOYL)
L29           0 SEA ABB=ON  PLU=ON  (3(W)(NITRATOPIVALOYL OR NITRATOPIVALOY
                L))(S)(PIVALOYL CYSTEIN#)

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
     JICST-EPLUS, JAPIO' ENTERED AT 12:43:26 ON 15 APR 2005
                D KWIC L22
L30          10 SEA ABB=ON  PLU=ON  L22 AND CYSTEIN#
                D KWIC
                D KWIC 2-3
L31           0 SEA ABB=ON  PLU=ON  (L16 OR L17 OR L18) AND (NITRATOPIVALOY
                L OR NITRATO PIVALOYL)
L32          30 SEA ABB=ON  PLU=ON  (L16 OR L17 OR L18) AND (TREAT? OR
                THERAP? OR PREVENT?)(5A)((PEPTIC OR GASTRODUODEN? OR
                GASTR? DUODEN? OR MARGINAL)(5A) UCLER? OR (GASTROINTESTIN?
                OR GASTR? INTESTIN? OR INTESTIN? OR GASTR## OR STOMACH)(5A)
                (DISORDER OR DISEAS?))
L33          24 DUP REM L32 (6 DUPLICATES REMOVED)
                D 1-24 IBIB ABS

     FILE 'HOME' ENTERED AT 12:48:16 ON 15 APR 2005
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